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Risk factors for and Strategies to Prevent Complications of Endoscopic Retrograde Cholangiopancreatography

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2021

ISSN 1651-6206
ISBN 978-91-513-1232-3
URN urn:nbn:se:uu:diva-445875

Dissertation presented at Uppsala University to be publicly examined in H:son-Holmdahlsalen, Ing 100, Akademiska Sjukhuset, Uppsala, Friday, 17 September 2021 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Riadh Sadik (Göteborgs Universitet).

Abstract

Syrén, E.-L. 2021. Risk factors for and Strategies to Prevent Complications of Endoscopic Retrograde Cholangiopancreatography. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1752. 79 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1232-3.

Aim: The overall aim of this thesis was to study risk factors for and strategies to prevent complications of Endoscopic Retrograde Cholangiopancreatography (ERCP).

Methods: Prospectively registered data from the Swedish National Quality Register for Gallstone Surgery and ERCP (GallRiks) 2006-2018 were retrospectively retrieved and reviewed. In Study I, ERCP procedures performed for common bile duct stones (CBDS), were analysed and cross-checked with the National Patient Register (NPR) in order to assess risk factors for post-ERCP pancreatitis (PEP). In Study II, different techniques for CBDS clearance over time at different hospital levels and the effectiveness and safety of postoperative rendezvous ERCP compared to intraoperative rendezvous ERCP were studied. In Study III, the rate of postoperative cardiovascular events in CBDS-patients treated with ERCP only, cholecystectomy only, cholecystectomy followed by delayed ERCP, cholecystectomy together with ERCP, or ERCP followed by delayed cholecystectomy were analysed. In Study IV, associations between ERCP success and complications, and endoscopist- and centre case-volumes regarding procedures for CBDS, and suspected or confirmed malignancy were analysed.

Results: Women, patients<65 years, patients with hyperlipidaemia, and those with a previous history of recent acute pancreatitis had a higher risk for PEP, while patients with diabetes had a lower risk (all $p<0.05$). Intraoperative ERCP increased during the period of the study, whereas preparation for postoperative ERCP decreased. CBDS management differed between different hospital levels. Total rate of intra- and postoperative complications as well as intraoperative bleeding, postoperative bile leakage, and postoperative infection with abscess were higher in the postoperative rendezvous ERCP group (all $p<0.05$). However, PEP, postoperative bleeding, cholangitis, percutaneous drainage, antibiotic treatment, ICU stay, readmission/reoperation within 30 days, and 30-day mortality did not differ between the groups. Nor did risk for cardiovascular complication or death within 30 days differ between patients treated for CBDS by cholecystectomy and/or ERCP. A high endoscopist case-volume was associated with higher successful cannulation rate and lower PEP rate ($p<0.05$). Centres with a high annual case-volume were associated with higher successful cannulation rates ($p<0.05$).

Conclusions: Age, sex, hyperlipidaemia, and previous history of recent acute pancreatitis all increased the risk for PEP while diabetes reduced the risk. Techniques for management of CBDS discovered at cholecystectomy have changed over time and differ between hospitals levels. Though intraoperative rendezvous ERCP is the method of choice, postoperative rendezvous ERCP is an acceptable alternative when adequate ERCP resources are lacking or limited. Primary ERCP as well as cholecystectomy for CBDS may be performed with acceptable safety. Higher endoscopist- and centre case-volumes lead to safer and more successful ERCP.

Keywords: ERCP, rendezvous ERCP, post-ERCP pancreatitis, choledocholithiasis, cardiovascular complications, case-volume

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ISSN 1651-6206
ISBN 978-91-513-1232-3
URN urn:nbn:se:uu:diva-445875 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-445875)

“To struggle and to understand. Never the last without the first. That is the law.”

George Herbert Leigh Mallory (18 June 1886 – 8 or 9 June 1924)

British teacher, explorer, and mountaineer

“ERCP is most dangerous for people who need it least”

Peter B. Cotton (born 1939),

British Gastroenterologist

To Johan

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Syrén E, Eriksson S, Enochsson L, Eklund A, Sandblom G. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography
BJS Open. 2019 Apr 2;3(4):485-489. doi: 10.1002/bjs5.50162. eCollection 2019 Aug.BJS Open. 2019. PMID: 31406957

II Syrén E, Sandblom G, Eriksson S, Eklund A, Isaksson B, Enochsson L. Postoperative rendezvous endoscopic retrograde cholangiopancreaticography as an option in the management of choledocholithiasis. Surg Endosc. 2020 Nov;34(11):4883-4889. doi: 10.1007/s00464-019-07272-1. Epub 2019 Nov 25.Surg Endosc. 2020. PMID: 31768727

III Syrén E, Enochsson L, Eriksson S, Eklund A, Isaksson B, Sandblom G. Cardiovascular complications after common bile duct stone extrations. Surg Endosc. 2020 Jul 1. doi: 10.1007/s00464-020-07766-3. Online ahead of print.Surg Endosc. 2020. PMID: 32613302

IV Syrén E, Sandblom G, Enochsson L, Eklund A, Isaksson B, Österberg J, Eriksson S. Outcome of endoscopic retrograde cholangiopancreatography related to case-volume.
Submitted

Contents

Abbreviations

ASA	American Society of Anesthesiologists
CBDS	Common Bile Duct Stones
CH	County/Community Hospital
CI	Confidence Interval
DASE	Dilation-Assisted Stone Extraction
EHL	Electrohydraulic Lithotripsy
ERCP	Endoscopic Retrograde Cholangio- pancreatography
EST	Endoscopic Sphincterotomy
ESWL	Extracorporeal shock wave lithotripsy
EUS	Endoscopic Ultrasonography
GallRiks	The Swedish National Quality Register for Gallstone Surgery and ERCP
ICD	International Classification of Diseases
IOC	Intraoperative Cholangiography
LAC	Laparoscopic Cholecystectomy
LC	Laparoscopic Choledochotomy
LERV	Laparo-endoscopic Rendezvous
LTSE	Laparoscopic Transcystic Stone Extraction
MRCP	Magnetic Resonance Cholangiopancreatography
NPR	National Patient Register
NOAK	Non-Vitamin K Oral Anticoagulants
NSAID	Non-Steroidal Anti-inflammatory Drugs
OR	Odds Ratio
OCBDE	Open Common Bile Duct Exploration
PSC	Primary Sclerosing Cholangitis
PEP	Post-ERCP Pancreatitis
PTC	Percutaneous Transhepatic Cholangiography
PTBD	Percutaneous Transhepatic Biliary Drainage
PTE	Pulmonary Thromboembolism
SEMS	Self-Expandable Metal Stents
SOD	Sphincter of Oddi Dysfunction
TRH	Tertiary Referral Hospital
UCR	Uppsala Clinical Research Centre

Introduction

Since 2007, when I became a specialist in General Surgery, my clinical work has focused on Endoscopic Retrograde Cholangiopancreatography (ERCP) and advanced endoscopy. Over the last decade there has been considerable technical progress in advanced endoscopy. Minimally invasive methods for imaging and treating patients with diseases of the upper gastrointestinal tract such as biliary stones and malignancy, have become methods of choice while some open surgical procedures are seldom performed today. In Sweden, intraoperative rendezvous ERCP has become the predominating method for managing choledocholithiasis detected at cholecystectomy, and peroral cholangiopancreatoscopy is now a natural part of the ERCP procedure.

Unfortunately, ERCP complications are still quite common and sometimes life-threatening despite technical progress and national and European treatment guidelines. In the Swedish National Quality Register for Gallstone Surgery and ERCP (GallRiks), which started 2005, the frequency of the most common surgical ERCP complication, Post-ERCP Pancreatitis (PEP), has remained constant over the years. In my research I have chosen to focus on risk factors for ERCP complications and how to avoid them.

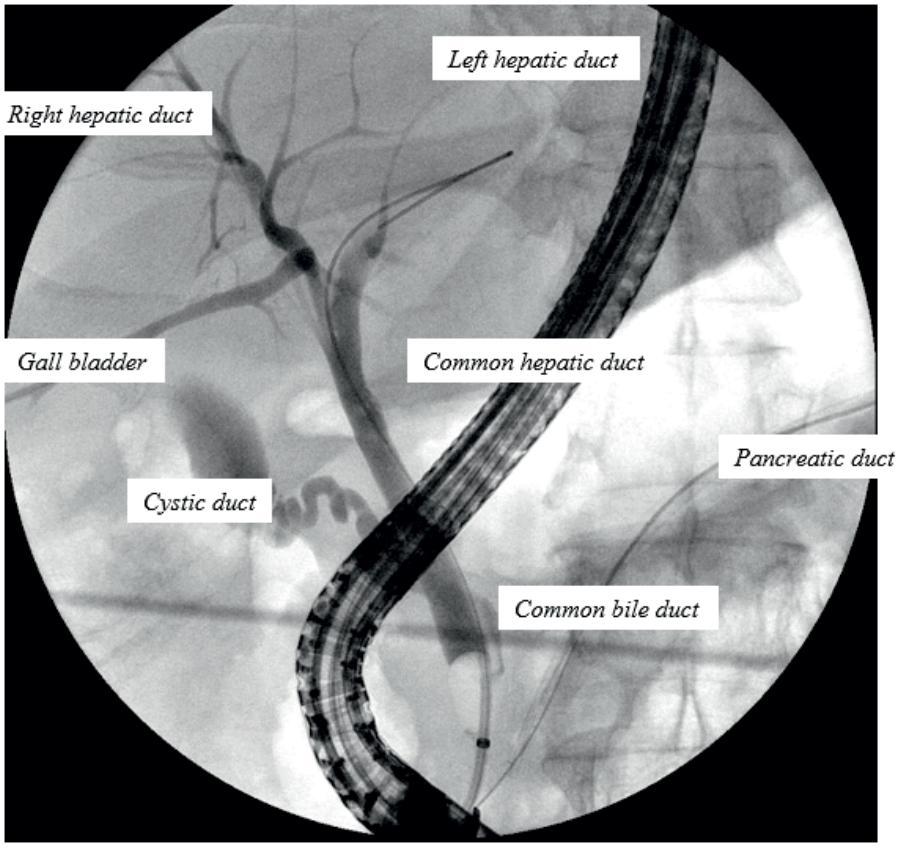


Figure 1. Cholangiopancreatogram.

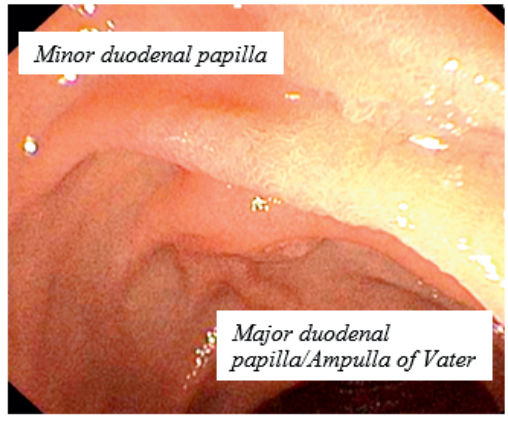


Figure 2. Minor and Major papilla.

Background

Common bile duct stones, cholecystectomy and intraoperative cholangiography

The lifetime risk of developing gallstones is approximately 20%. Of those who have gallstones >20%, or about 2–3% per year, develop symptoms or complications secondary to the stones. Risk factors for gallstones include female sex, age, pregnancy, physical inactivity, obesity and over-nutrition [1-4]. Common bile duct stone (CBDS) is relatively frequent with a prevalence of 10-20% in patients with gallstones. CBDSs are associated with serious conditions, such as obstructive jaundice, acute cholangitis, and acute pancreatitis [5]. Transabdominal ultrasound combined with adequate assessment of clinical symptoms and elevated liver function tests, is often used as a first-line diagnostic tool for CBDS. In cases with persistent clinical suspicion but insufficient evidence of stones on abdominal ultrasonography, endoscopic ultrasonography (EUS), or magnetic resonance cholangiopancreatography (MRCP) are the methods of choice (sensitivity 97% vs. 90% and specificity 87% vs. 92% for EUS and MRCP, respectively) [6, 7].

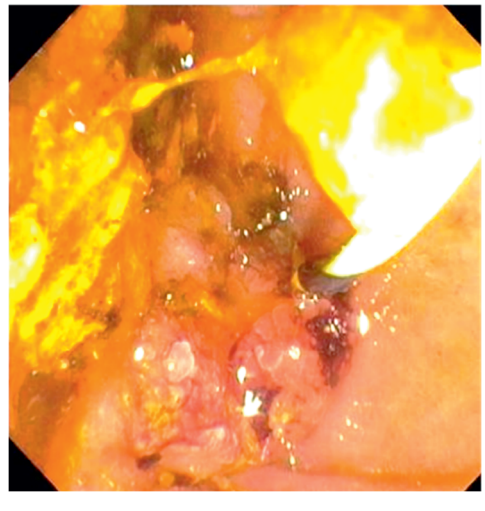


Figure 3. ERCP as treatment for CBDS.

Laparoscopic cholecystectomy (LAC) is the method of choice for treatment of gallstone disease worldwide. In Sweden alone, 13 000 cholecystectomies are performed each year, predominantly using the laparoscopic technique [8-10]. Intraoperative cholangiography (IOC) has been shown to be effective in visualising the anatomy of the biliary tree and detecting CBDS, found at 10-15% of operations [8-13].

Four strategies to manage CBDS are available: preoperative endoscopic retrograde cholangiopancreatography (ERCP) plus LAC; LAC plus laparoscopic stone extraction; LAC plus intraoperative ERCP, also called rendezvous; and, finally, LAC plus postoperative ERCP. The optimal method for

Figure 4. LC plus LERV at Akademiska Hospital, Uppsala.

managing CBDS as well as the timing of treatment is still the subject of debate, and treatment regimen decisions are largely based on local traditions [14]. A meta-analysis comparing preoperative ERCP plus LAC, LAC plus LC, LAC plus intraoperative laparo-endoscopic rendezvous (LERV), and LAC plus postoperative ERCP concluded that the combination of LAC and LERV had the lowest rate of complications and appeared to be the most successful [15]. One-stage procedures, if logistically possible, are preferable since they result in shorter hospital stay and a higher success rate [16, 17].

Leaving common bile duct stones in *situ*

Even if the natural history of CBDSs is not fully understood there are data and guidelines advocating an active approach to clear the common bile duct [18, 19]. A GallRiks study in which 3969 patients with CBDSs on IOC were included concluded that if CBDSs are detected, they should be extracted to avoid late complications. Within 4 years follow-up, 25.3% of patients with CBDSs in situ developed complications (pancreatitis, cholangitis, or obstruction of the bile duct) vs. 12.7% of patients who had undergone CBDS removal (odds ratio [OR] 0.44, 95% CI 0.35–0.55). The likelihood of an unfavourable outcome increased with size of CBDS, but the complication rate for CBDS less than 4 mm was still 5.9% vs. 8.9% for larger CBDSs (OR 0.52, 95% CI 0.34–0.79) [20]. However, previous studies have shown that many small stones pass into the duodenum spontaneously without serious complications. They may thus be left in situ, thereby sparing the patient a potentially unnecessary and harmful intervention [21-23]. A conservative approach can therefore be considered in fragile patients at high risk for complications of surgical or endoscopic CBDS extraction [19].

Laparoscopic transcystic stone extraction and laparoscopic choledochotomy

Established options to treat choledocholithiasis include Laparoscopic Transcystic Stone Extraction (LTSE) and Laparoscopic Choledochotomy (LC). Both techniques have some limitations and are technically challenging, but have been shown to be effective in the treatment of bile duct stones, with low morbidity compared to the traditional alternative of Open Common Bile Duct Exploration (OCBDE) the use of which has decreased in recent years [24-29]. Laparoscopic cholecystectomy plus LBCDE appears to reduce the risk for acute pancreatitis but may be associated with a higher risk for biliary leakage [15].

Endoscopic retrograde cholangiopancreatography

Endoscopic Retrograde Cholangiopancreatography (ERCP) is an effective method to investigate and treat diseases of the biliary and pancreatic ducts such as choledocholithiasis and malignancy. In Sweden, ERCP has become method of choice for treatment of CBDS detected by IOC, and about 9000 ERCPs are performed each year [8-10]. In an unselected population-based settings, successful cannulation is achieved in >85% of cases [9, 30]. The complexity of ERCP, however, ranges from uncomplicated extraction of small stones to extremely challenging procedures such as hilar stenting, Electrohydraulic Lithotripsy (EHL) for difficult stones, or oral cholangiopancreatoscopy. ERCP complexity can be graded according to Schutz's criteria [31].

Figure 5. ERCP in a patient with Primary Sclerosing Cholangitis.

Table 1. Schutz classification of complexity of ERCP.

Grade 1: simple diagnostic ERCP	Standard diagnostic cholangiogram/pancreatogram
Grade 2: simple therapeutic ERCP	Standard biliary sphincterotomy; removal of 1-2 small common duct stones (≤ 1 cm); nasobiliary drain placement
Grade 3: complex diagnostic ERCP	Diagnostic cholangiogram/pancreatogram, Billroth II anatomy, biliary/pancreatic cytology, minor papilla cannulation
Grade 4: complex therapeutic ERCP	Multiple (≥ 3) or large (> 1 cm) common duct stones, cystic duct or gallbladder stone removal, common duct stricture dilation, common duct stenting (plastic or metal)
Grade 5: very advanced ERCP	Precut biliary sphincterotomy, stone removal with lithotripsy (any type), intrahepatic stone removal/stricture dilation, biliary therapy, Billroth II anatomy, cholangioscopy All forms of pancreas therapy (pancreatic sphincterotomy, stenting or stone removal, any minor papilla therapy), any pseudocyst drainage (transpapillary, transgastric, transduodenal), pancreatoscopy

Another classification system for the complexity of ERCP is the Cotton classification from 2011. This system is based on experienced endoscopists' complexity grading of different endoscopic procedures that also takes into account the endoscopist's own experience [32].

Table 2. Cotton classification of complexity of ERCP.

Grade 1	Diagnostic ERCP, brush cytology
Grade 1.5	Stent exchange, stent extraction
Grade 2	Biliary leak, CBDS <10mm, extrahepatic stent, prophylactic pancreatic stent
Grade 3	Pancreatic stones <5mm, CBDS >10mm, migrated stents, pancreatitis, SOD, papilla minor, pancreatic strictures, hilar strictures, intrahepatic stones, intraductal imaging (cholangio/pancreatography)
Grade 3.5	Migrated pancreatic stents
Grade 4	Pancreatic stones >5mm or fixed stones, intraductal therapy (EHL), ampullectomy, Roux-en-Y, pseudocysts, necrosectomy
+ 1 point for	Billroth II anatomy, child <3 years, previously failed procedure or procedure performed outside working hours

The lack of validation of existing complexity grading scales, and the need to compare results from different endoscopic centres and allocate resources, re-

quires a new ERCP complexity grading scale. An example of a modern grading scale is the H.O.U.S.E. classification which was first presented in 2017 [33]. This was developed at the Karolinska University Hospital, Huddinge, to motivate increasing costs and procedure times, thereby optimising resources regarding advanced endoscopic procedures. H.O.U.S.E. is an abbreviation of the first letter of the name of the hospital Huddinge followed by the first letters of the names of the authors (Olsson, Urban, Swahn, and Enochsson). The scale was designed after a review of the medical records of every patient undergoing ERCP at Karolinska Hospital 2009-2011 (1931 procedures). The H.O.U.S.E and Cotton scales classify procedure complexity into three grades. Since all ERCP procedures were registered in GallRiks, correlations could be made between grading systems and procedure-related variables and outcome. The H.O.U.S.E. score was associated with procedure time, procedure complexity, and frequency of adverse events [33].

Table 3. H.O.U.S.E. classification of complexity of ERCP.

H.O.U.S.E. 1	Diagnostic ERCP, EST, CBDS, single stent, brush cytology, intraoperative rendezvous ERCP
H.O.U.S.E. 2	Intrahepatic stone, multiple stents, pancreatic ERCP, PSC or liver transplantation, intrahepatic interventions, prophylactic pancreatic stent, "caged" papilla, ERCP with ESWL
H.O.U.S.E. 3	Pancreatic sphincterotomy and lithotripsy, spy-glass, mother-baby-scopy, EHL, multiple pancreatic stents, papillectomy, confocal endoscopy, PTC- or EUS-rendezvous Altered anatomy: Billroth II, Roux-en-Y, Whipple, Gastric bypass, ERCP via enteroscopy

ERCP has traditionally been performed as a two-stage procedure, either preoperative ERCP prior to cholecystectomy, or cholecystectomy followed by postoperative ERCP. Since 4-18% of attempted ERCPs fail due to inability to cannulate the bile duct, and since ERCP may lead to serious complications, the intraoperative laparo-endoscopic rendezvous (LERV) became the method of choice in most hospitals [8-10].

Intraoperative rendezvous ERCP

The technique of LERV was first described in 1993 by Deslandres et al [34]. In this technique access to the common bile duct is facilitated by a guidewire, which is introduced intraoperatively, under fluoroscopic control, antegrade to the duodenum through the cystic duct. According to GallRiks data, the success rate of passing the transcystic guidewire into the duodenum is >80% and there is less traumatic manipulation of the papilla Vateri [35, 36]. Several studies have shown intraoperative rendezvous ERCP to have a high rate of CBDS

clearance with few complications, particularly post-ERCP pancreatitis, compared to conventional ERCP [36-45].

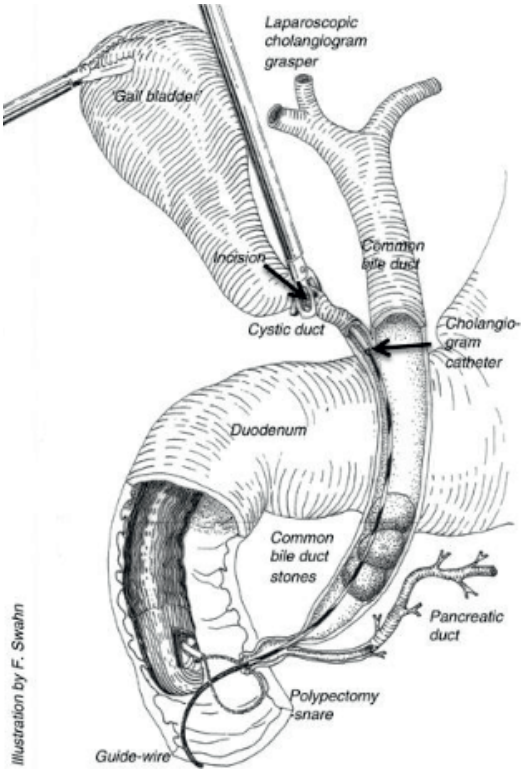


Figure 6. Intraoperative rendezvous ERCP, *drawing by Fredrik Swahn.*

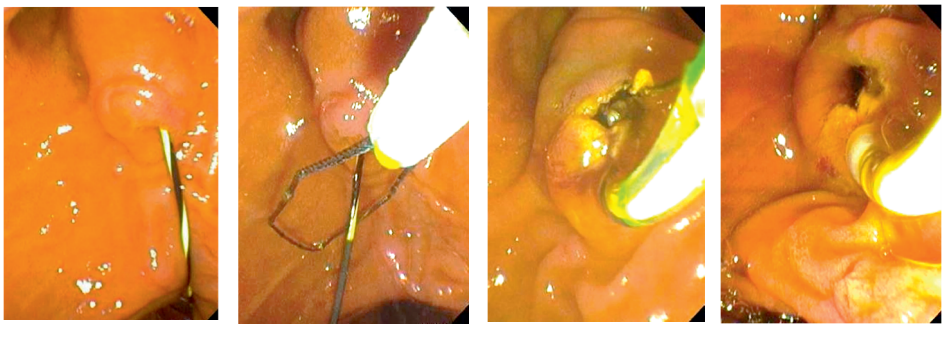


Figure 7. Intraoperative rendezvous ERCP.

Postoperative rendezvous ERCP

In postoperative rendezvous ERCP, the antegrade transcystic guidewire is passed into the duodenum and anchored to the cystic duct with clips. The other end of the guidewire is then passed through the abdominal wall and attached by tape to the skin, leaving the guidewire in situ. The cholecystectomy is then completed and the rendezvous ERCP conducted at a later second session, usually within 1-2 days.

Intraoperative rendezvous ERCP is preferred since it is associated with shorter hospital stay, reduced cost, and appears to have lower morbidity than postoperative rendezvous ERCP [14, 46-48]. Postoperative rendezvous ERCP is an alternative to intraoperative ERCP in situations where adequate endoscopic resources are limited or lacking.

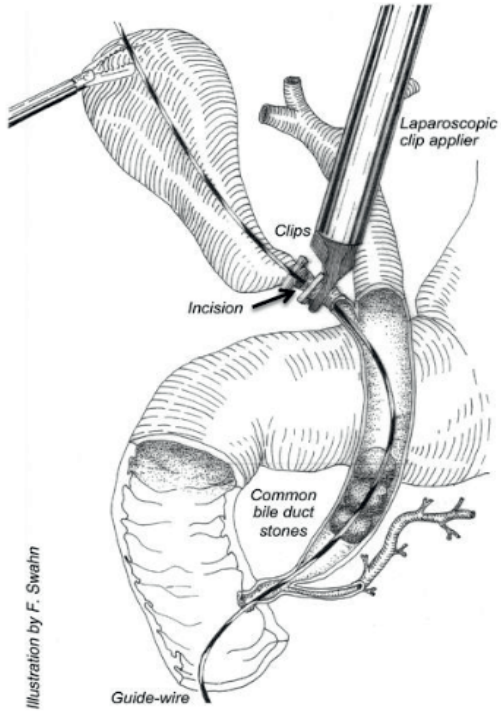


Figure 8. Postoperative rendezvous ERCP, *drawing by Fredrik Swahn.*

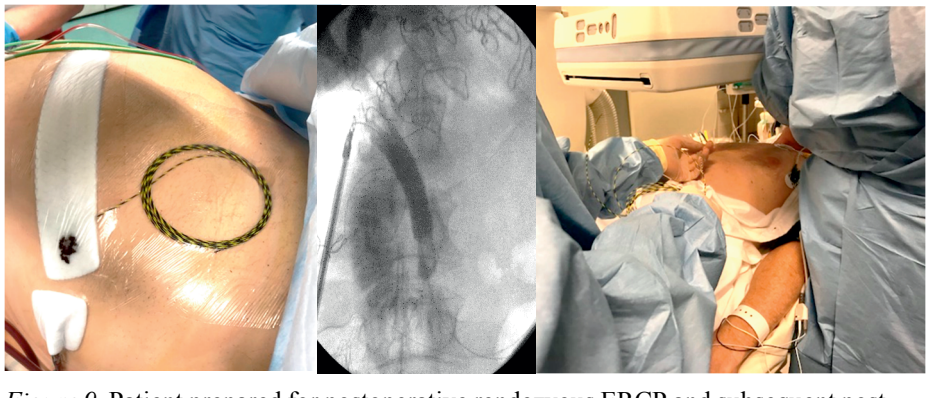


Figure 9. Patient prepared for postoperative rendezvous ERCP and subsequent postoperative rendezvous ERCP.

Complications of ERCP

Of all the procedures that endoscopists perform on a regular basis, ERCP is that associated with the greatest risk, with a complication rate of 10-15%. Most complications are recognized during or shortly after ERCP, but some complications such as bleeding following sphincterotomy are delayed. The risk for adverse events in ERCP depends on patient risk factors, risk factors related to the technical procedure and experience of the endoscopist and team [8, 9, 43, 49, 50]. The indications and benefits of ERCP must balance potential harm to the patient.

Post-ERCP pancreatitis

The most common complication described after ERCP is Post-ERCP Pancreatitis (PEP), with a frequency of 3.5-5% [9, 51, 52] and in some studies even 9.7% [53]. PEP is usually divided into 3 categories according to Cotton et al, where mild and moderate PEP constitute about 90% [49]. Mortality after PEP is 0.7% and depends on the severity [53].

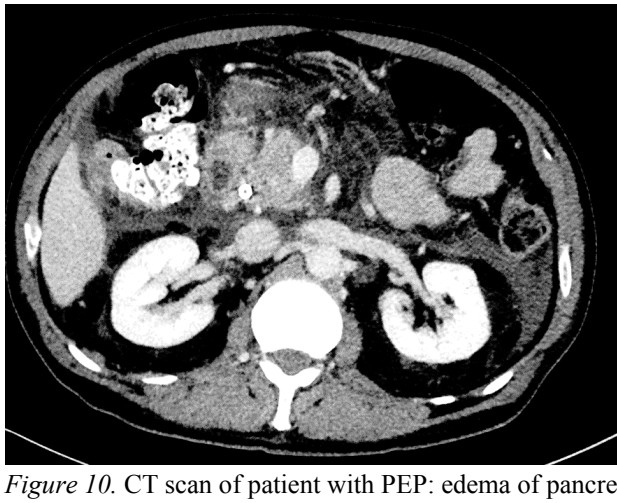


Figure 10. CT scan of patient with PEP: edema of pancreatic head, metal stent in ductus choledochus (common bile duct).

Table 4. Cotton classification of severity of post-ERCP pancreatitis.

Mild Pancreatitis	Abdominal pain plus p-amylase elevated ≥3 times normal value requiring hospital admission or prolongation of planned admission up to 3 days.
Moderate Pancreatitis	Requires hospitalisation for 4-10 days.
Severe Pancreatitis	Requires hospitalisation for >10 days plus signs of local or systemic complications (necrosis, pseudocysts, multi-organ failure), or requires surgical or percutaneous intervention.

There are a number of PEP risk factors described in the literature, and the risk depends on both technical- and patient-related factors [49-51, 54-57]. Although PEP is widely accepted as the primary outcome measure following ERCP, the risk factors for PEP are like other adverse events such as bleeding, perforation, and other procedure-related complications. PEP may thus be considered a surrogate endpoint for the safety and success of ERCP.

Table 5. Examples of risk factors for post-ERCP pancreatitis.

Examples of patient-related risk factors for PEP
Sphincter of Oddi Dysfunction (SOD), female gender, previous pancreatitis including PEP, younger age, no chronic pancreatitis, normal bilirubin level, non-dilated bile duct

Examples of procedure-related risk factors for PEP
Cannulation>10 minutes, pancreatic guidewire passage, or contrast injection, Precut sphincterotomy, pancreatic sphincterotomy, biliary balloon-sphincter dilation, failure of CBDS clearance, intraductal ultrasound

Acute pancreatitis

The most common causes of acute pancreatitis are biliary stone and alcohol abuse. Other conditions such as long-term haemodialysis or peritoneal dialysis, hepatic disease, hyperlipidaemia, hypercalcaemia, and diabetes, that are known to increase the risk for acute pancreatitis, may also be risk factors for PEP [58-68].

Bleeding, cholangitis and perforation

Besides PEP, other well-known complications of ERCP are bleeding, cholangitis, and perforation.

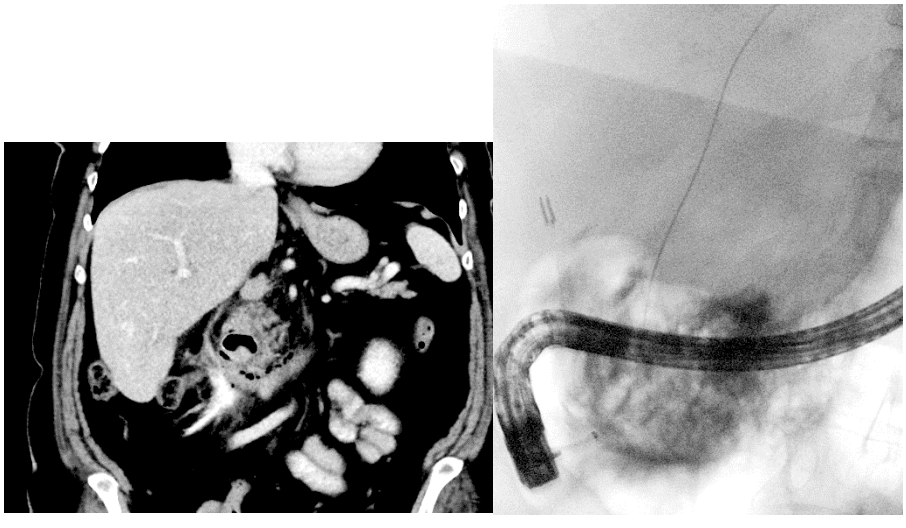


Figure 11. Retroperitoneal perforation during ERCP with leakage of gas and contrast.

Clinically significant bleeding occurs in 1-3% of ERCPs. It may occur immediately but is often delayed up to 2 weeks [9, 49, 50]. Bleeding is graded as mild (no blood transfusion), moderate (up to 4 units of blood), or severe (>5 units of blood or surgical/angiographic intervention) [49]. Risk factors for bleeding include coagulopathy, anticoagulation therapy and in some studies precut sphincterotomy [49, 50]. Other studies, however, have not shown any increased risk for bleeding when early precut is performed for difficult biliary access [69, 70].

Cholangitis is reported in 0.5-5% of ERCPs, and bacteraemia in up to 27% of procedures [71, 72]. Biliary infection may be a result of failed complete drainage after the ERCP procedure. Other risk factors include hilar cholangiocarcinoma and primary sclerosing cholangitis (PSC) [9, 49]. Cholangitis is graded as mild (temperature >38 °C for 24-48 hours), moderate (≥3 days in-hospital care or ERCP/PTC (Percutaneous Transhepatic Cholangiography) intervention), or severe (septic shock or need for surgical intervention) [49].

Perforation sometimes occurs when the guidewire or catheter penetrates the wall of the pancreatic or biliary ductal system. The exact frequency of perforation is not known since they are seldom reported and adverse consequences for the patient are rare [73]. Duodenal perforation related to sphincterotomy occurs in <1% of ERCPs [9, 49, 50]. This perforation is retroperitoneal and can be managed conservatively with antibiotics. The risk for sphincterotomy-related perforation increases if the cut is large and extends beyond "1-2 o'clock" or in cases of repeated sphincterotomy, but does not seem to increase

in cases where early precut has been performed [69, 70]. Perforation following pancreatic sphincterotomy either at the main or minor papilla is extremely rare [74]. Perforations are classified into mild (<3 days of hospital care and conservative treatment), moderate (4-10 days of hospital care) or severe (>10 days in hospital and need for surgical intervention or drainage) [49]. Routine CT investigations in asymptomatic patients after uncomplicated sphincterotomy have shown retro- or periduodenal gas in up to 10% of cases [75].

Figure 12. Perforation of guide wire in bile duct with extravasation of contrast.

The risk for perforation, bleeding or cholangitis does not differ between ERCP-patients with or without a periampullary diverticulum [76].

Cardiovascular complications

Transient cardiac dysrhythmias and hypoxia are usually seen and managed during ERCP procedures, and only rarely do they result in clinical consequences or adverse events. Cardiovascular complications and pulmonary thromboembolism (PTE) occur in 0.5-1% of ERCPs and laparoscopic cholecystectomies [9, 10, 50, 77-80]. The prevalence of CBDS increases with age. This complicates management since comorbidity and frailty increase the risk for intervention-related complications and death [81-83]. Cardiovascular disease and biliary stone disease share risk factors such as obesity, hypertension, diabetes, dyslipidaemia and cigarette smoking [84-86]. There also appears to be an association between gallstone disease and cardiovascular disease [87]. Though early cholecystectomy appears to be safe in the elderly, there is a tendency to choose a minimally-invasive treatment method such as ERCP when it comes to elderly frail patients with high comorbidity [88].

Other ERCP complications

Other complications related to ERCP include endoscopic perforation of the oesophagus, stomach, or duodenum. The risk for these perforations is usually low, about 1:1000, but increases in patients with altered anatomy such as after Billroth II gastrectomy or when stenosis is present in the upper gastrointestinal

tract [73, 89]. There are also rare reports of penetration and perforation of the duodenum, small bowel or colon after migration of plastic stents from the bile duct [90, 91].

Other examples of complications are basket impaction during an attempt to remove a large stone from the bile duct, cholecystitis caused by self-expandable metal stents (SEMS), contrast injection into the portal venous system, and in rare cases pseudomonas infection due to inadequate disinfection and cleaning of the duodenoscope. Thirty-day mortality after ERCP is about 0.5% [9, 10, 50, 92, 93].

Endoscopic sphincterotomy (EST) was previously thought to be a risk factor for the development of cholangiocarcinoma due to reflux of gut bacteria into the biliary system, though recent studies have not seen an increase in cancer risk after EST [94, 95].

Figure 13. Late perforation of plastic stent through duodenal wall opposite to the major papilla.

Stent dysfunction

Endoscopic biliary stent placement is an effective treatment for patients with benign or malignant biliary obstruction causing jaundice and/or cholangitis [96]. If the decision is made to proceed with biliary drainage in patients with malignant distal biliary obstruction and who are planned for curative resection, the endoscopic route is preferred to percutaneous transhepatic biliary drainage (PTBD) because of better patient survival and fewer peritoneal/liver recurrences in the endoscopic group [97-99]. Regarding palliative treatment of patients with hilar and extrahepatic malignant biliary obstruction, ERCP has a lower adverse event rate, shorter time in hospital, and lower cost

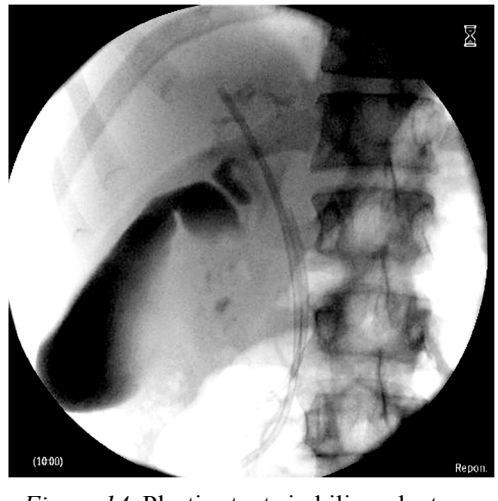


Figure 14. Plastic stents in biliary duct.

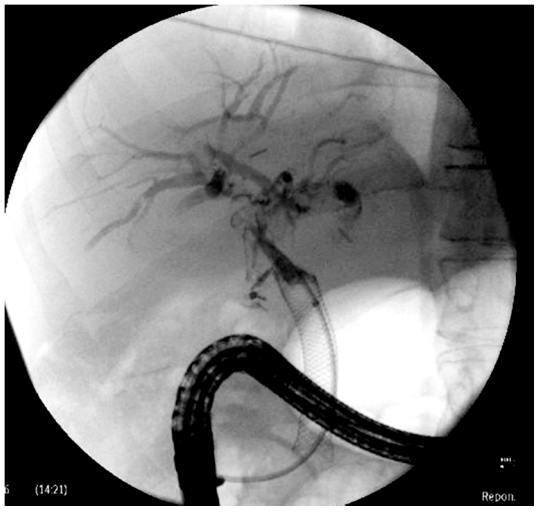


Figure 15. Leakage in biliary duct anastomosis after liver transplantation. treated with SEMS

compared to PTBD [100], as well as lower morbidity and mortality rates compared to surgical bypass [101, 102]. The diagnosis of stent dysfunction is usually based on a combination of clinical criteria and a less than 20% fall in serum bilirubin following stent insertion i.e., failed biliary drainage with development of cholangitis and jaundice. Sometimes, transabdominal ultrasound is needed to confirm stent failure [101, 103].

Two types of stent are routinely used in current practice; plastic stents and self-expanding metal stents (SEMS). Several studies have shown that metal stents are associated with significantly longer stent patency and lower re-intervention rate in the palliative management of malignant bile duct obstruction, compared to plastic stents [104-106]. This results in shorter hospital stay, reduction in frequency of complicating diseases due to stent dysfunction, and improvement in quality of life [107, 108]. Moreover, some studies have shown that metal stents are associated with longer survival compared to plastic stents [109, 110]. The median patency times of metal and plastic stents in patients with distal malignant obstruction were found to be longer than 8 months and 4 to 6 months, respectively [109, 111]. The median patency times of metal and plastic stents in patients with hilar cholangiocarcinoma were found to be 3 to 6 months and 1 to 2 months, respectively [111, 112]. SEMS is the method of choice in potentially curable patients with obstructive jaundice while waiting for surgery or in a neoadjuvant situation, because stent dysfunction and stent-related complications are fewer compared to plastic stents [96, 113, 114]. Covered SEMS have a lower risk for tumour ingrowth but a higher risk for stent migration and tumour overgrowth compared to uncovered SEMS. However, meta-analyses show largely equivalent results regarding

Figure 16. Dysfunctional plastic stents.

Figure 17. Covered SEMS.

proportions of patients with stent dysfunction, overall complications, and patient survival when comparing covered, partially covered, and uncovered SEMS [115-117]. There does not seem to be difference in risk for cholecystitis after insertion of covered vs. uncovered SEMS [117, 118].

Prevention of ERCP complications

Anticoagulants such as warfarin or non-vitamin K oral anticoagulants (NOAKs), must be discontinued prior to ERCP, and any coagulopathy managed. Pure-cut diathermy has been shown to be associated with a higher risk for bleeding compared to blended diathermy [119]. Large balloon dilation in combination with sphincterotomy for treatment of large stones, DASE (Dilatation Assisted Stone Extraction), is associated with less risk for bleeding compared to plain sphincterotomy [120].

Carbon dioxide via the duodenoscope has not been shown to reduce the complication rate after ERCP, but causes less post-ERCP abdominal pain and is therefore recommended as part of the procedure [51].

Antibiotic prophylaxis

Evidence supporting prophylactic antibiotics to prevent infection after ERCP is limited, and meta-analyses are contradictory [121, 122]. The agents most commonly studied are cefotaxim and piperacillin. Even though the frequency of bacteraemia is less, antibiotic prophylaxis has not been shown to significantly prevent ERCP-induced cholangitis in unselected patients. The use of prophylactic antibiotics is recommended in patients where the risk for incomplete drainage of the bile duct is high, for example PSC patients and patients with a hilar tumour or where drainage is unsuccessful [51]. Immunosuppressed patients also seem to benefit from prophylaxis [123]. ERCP with concomitant cholangioscopy is associated with bacteraemia in up to 13.9% of

cases and infectious complications up to 9.7%. Thus antibiotic prophylaxis is recommended in this situation [124].

Prevention of post-ERCP pancreatitis

Difficult cannulation (several guidewire passages and contrast injections into the pancreatic duct, repeated cannulation attempts, and long time taken to reach the bile duct) is associated with an increased rate of ERCP-related complications [51, 125-131]. Difficult cannulation has been defined by Halttunen et al as fulfilling at least one of the following criteria:

≥5 cannulation attempts
≥5 minutes cannulation
≥2 passages of guidewire into the pancreatic duct.

When using this definition, difficult cannulation has been shown to increase the PEP rate fourfold probably because of oedema and trauma to the papilla [132]. A careful cannulation technique including use of a guidewire instead of the catheter and the use of contrast to identify the bile duct, has been shown to reduce the risk for PEP [133-135].

Figure 18. Double guidewire cannulation.

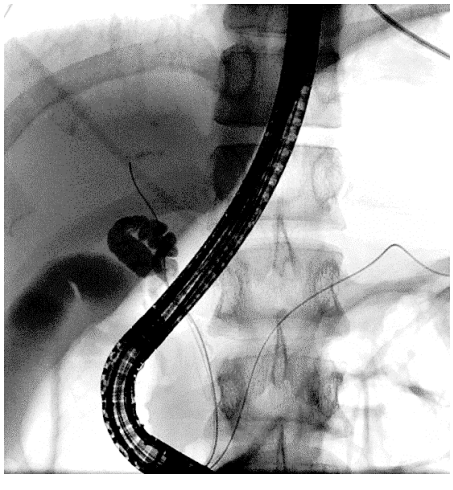


Figure 19. Cannulation of bile and pancreatic ducts.

Rendezvous-ERCP as a way to manage CBDS found at cholecystectomy is another way to reduce the risk for PEP [36, 41].

Some studies have shown an increased risk for PEP when precut sphincterotomy is performed. However, recent meta-analyses have concluded that there is a lower risk for PEP when precut is performed at an early stage in patients with difficult biliary access [136, 137].

If the guidewire passes into the pancreatic duct instead of the intended bile duct, this guidewire may be left in place and a second guidewire used to gain access to the biliary

ducts in the so called "double guidewire cannulation technique" [138-140]. As an alternative to the pancreatic guidewire-assisted technique, a pancreatic sphincterotomy, possibly with the help of a pancreatic stent, could help when cannulation of the bile duct is difficult. The complication rates of these manoeuvres are comparable to precut sphincterotomy [141-143]. In order to reduce the risk for PEP, it is recommended to leave a prophylactic pancreatic stent before completion of the ERCP [138, 144-146]. Several studies have shown the use of prophylactic pancreatic stents to reduce the risk for PEP, and guidelines recommend a 5 Fr diameter stent [51, 147].

Some studies indicate that the PEP rate is higher in cases when precut sphincterotomy is performed during ERCP compared to conventional sphincterotomy. This is probably a matter of timing since no increase in PEP rate has been shown if the precut is performed early on in the procedure [69, 148-151].

Non-steroidal anti-inflammatory drugs and post-ERCP pancreatitis

Since non-steroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A, an enzyme thought to play an important role in the pathogenesis of acute pancreatitis, studies have been conducted to assess the possible role of NSAIDs as a protective measure against PEP. Randomised studies and meta-analyses have shown that rectally administered indomethacin or diclofenac 100 mg as premedication before ERCP decreases the risk for PEP compared to placebo, particularly in high-risk patients [54, 152-160]. On the other hand, NSAIDs administered orally or intramuscularly have not been shown to be effective as protective against PEP [161, 162].

There are, however, prospective randomised controlled studies showing no difference in PEP rate between rectally administered diclofenac/indomethacin and placebo [153, 163-165]. A limitation of the meta-analyses published so far, regardless of conclusions, is that they include studies with relatively few subjects, different study designs, and varying proportions of high-risk patients. As a consequence of this, guidelines vary widely, and in 2016-2017 only 25% of ERCP-patients in Sweden were given NSAID as PEP prophylaxis [9].

Other pharmacological prevention of post-ERCP pancreatitis

Several agents have been studied regarding a possible protective effect against PEP, but results have been contradictory. Examples are: Protease inhibitors,

glyceryl trinitrate, octreotide, and somatostatin [51, 166-169]. Prophylactic antibiotics have not been shown to be effective against PEP [170].

Outcome of ERCP related to case-volume

Lack of experience has been shown to be associated with poor outcome in major surgical procedures [171]. Likewise, extensive training and high ERCP case-volume have been shown to correlate with high success rates in terms of successful cannulation with fewer complications [30, 57, 172-176]. Experienced endoscopists have lower complication rates and higher success rates than their less experienced colleagues, which emphasises the importance of education and training. Technical failure of ERCP has been shown to increase the complication rate three-fold [177, 178]. Several studies have shown that high-volume ERCP centres have better results and lower complication rates than low-volume centres [172, 173, 179, 180], though there are data indicating that high quality ERCP may be performed in low-volume units [181-183].
It is important to select patients with correct indications since ERCP is most hazardous for patients who need it the least. Potential benefits of the procedure must exceed potential risks. Centralisation of complicated ERCPs to high-volume centres with highly experienced endoscopists may well increase the safety and success of this procedure [184].

GallRiks

The studies in this thesis are mainly based on data from GallRiks (The Swedish National Quality Register for Gallstone Surgery and ERCP). GallRiks was started in 2005 under the direction of the Swedish National Board of Health and Welfare and the Swedish Surgical Society, and has since been administered by the Uppsala Clinical Research Centre (UCR). GallRiks covers around 90% of all cholecystectomies and ERCPs performed in Sweden with almost all hospitals participating. Data coverage is assessed by cross-linkage with the Swedish Hospital Discharge Register, and GallRiks is also linked to the Cause of Death Register. External validatation of GallRiks is regularly performed through periodic audits at each hospital once every three years. Complete match between medical records and the GallRiks data-base has been shown in 97.3% of ERCPs when results from the first 25 audited hospitals were analysed [185]. The validation process and national coverage rate are published each year. Registration in GallRiks is managed online via an internet platform (www.ucr.uu.se/gallriks) and data are entered by the endoscopist at the time of the procedure. Records include patient- and procedure-related data with the possibility to describe more than 100 different variables, as well as multiple-choice questions. Intraoperative complications are registered, and

when all variables are filled in, the online form is closed. Collection of follow-up data including intra- and postoperative complications is managed locally at each hospital by a specific coordinator (often a nurse or sometimes a secretary) 30 days after ERCP [8, 186, 187].

National Patient Register

The National Patient Register (NPR) collects data on healthcare of all patients admitted to hospital and in outpatient specialist care. It is maintained by the Swedish National Board of Health and Welfare. Though under-reporting of inpatient data is low, there has been a problem with outpatient care data, but this has improved greatly since 2001. A quality control of submitted data in the register is performed regularly, checking for quality and validity of personal registration number, hospital, and main diagnosis, amongst other things. If submitted data are suspected of being erroneous or invalid, new data are requested from the care-providers [188-190].

Rationale behind this thesis

The overall aim of this thesis was to study and to gain a deeper understanding of the complications and risk factors associated with ERCP, and any protective measures that may reduce these complications.

Aims

Paper I

To assess whether clinical variables and comorbidities influence the risk for PEP.

Paper II

The primary aim was to determine how various techniques for management of CBDS clearance in patients undergoing cholecystectomy have changed with time at tertiary referral hospitals (TRH) and county/community hospitals (CH). The secondary aim was to explore whether postoperative rendezvous ERCP is a safe, effective, and feasible alternative to intraoperative rendezvous ERCP in the management of CBDS.

Paper III

To compare the rate of postoperative cardiovascular events in patients with CBDS treated with the following: ERCP only; cholecystectomy only; cholecystectomy followed by delayed ERCP; cholecystectomy together with ERCP; or ERCP followed by delayed cholecystectomy.

Paper IV

To analyse the association between ERCP success and complication rates, and endoscopist- and centre case-volumes.

Methods

Paper I

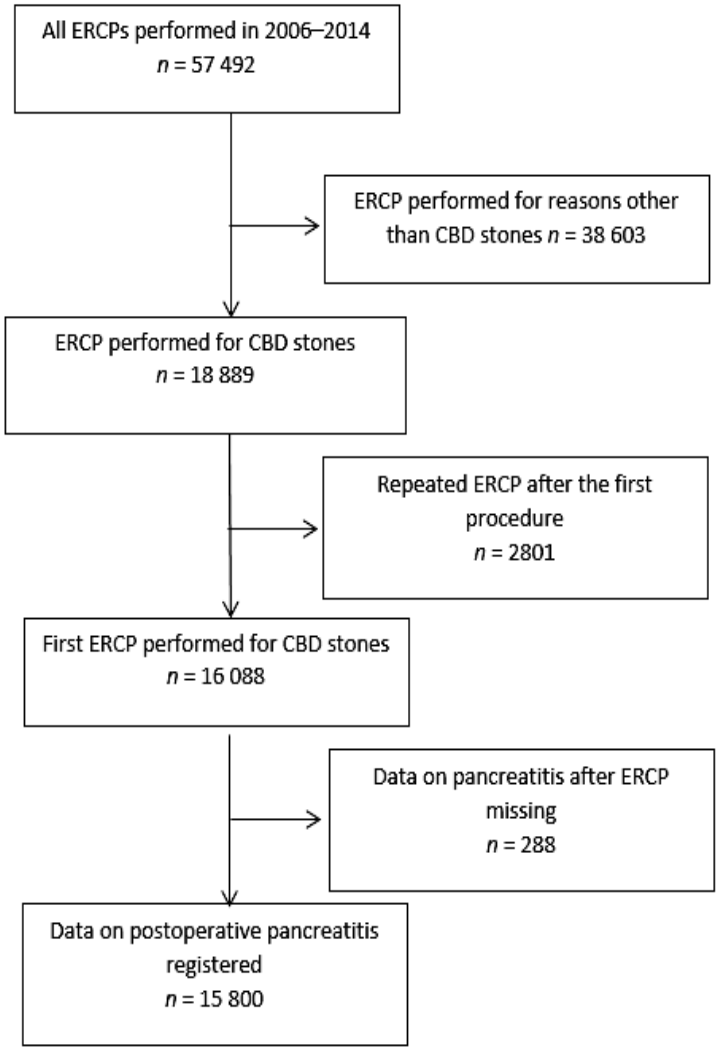


Figure 20. Flow diagram for the study. ERCP, endoscopic retrograde cholangio-pancreatography; CBD, common bile duct.

Data were retrieved from the Swedish Register for Cholecystectomy and ERCP (GallRiks) including all ERCP procedures performed 2006–2014 for common bile duct stones. A total of 15 800 procedures were identified and cross-checked. Univariable and multivariable logistic regression analyses were conducted with PEP as endpoint and the following covariables: age, gender, ASA grade, previous history of acute pancreatitis, diabetes, hyperlipidaemia, hypercalcaemia, kidney disease, and liver cirrhosis.

Paper II

Data were retrieved from the Swedish Register for Cholecystectomy and ERCP (GallRiks) 2006-2016. All cholecystectomies where CBDS were found at intraoperative cholangiography, and with complete 30-day follow-up (n=10386) were identified. Data concerning intraoperative and postoperative

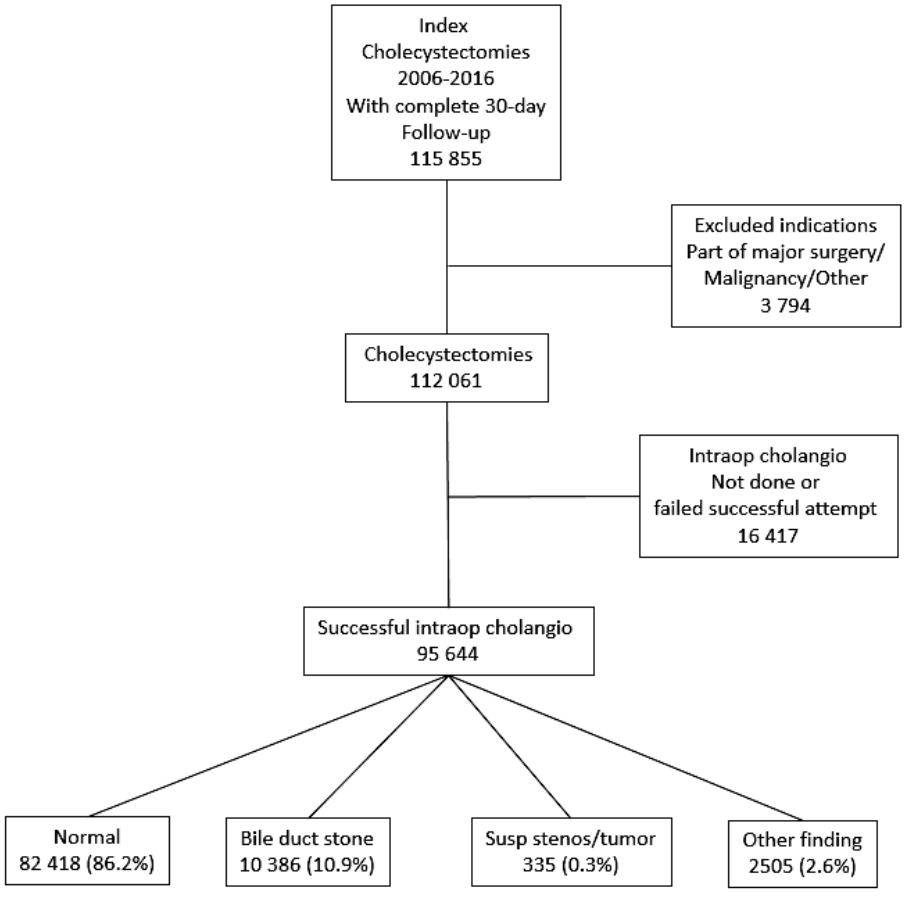


Figure 21. Flowchart cholecystectomies in Sweden 2006–2016.

complications, readmission, and reoperation within 30 days were retrieved for patients where intraoperative ERCP (n=2290) or preparation for postoperative ERCP was performed (n=2283).

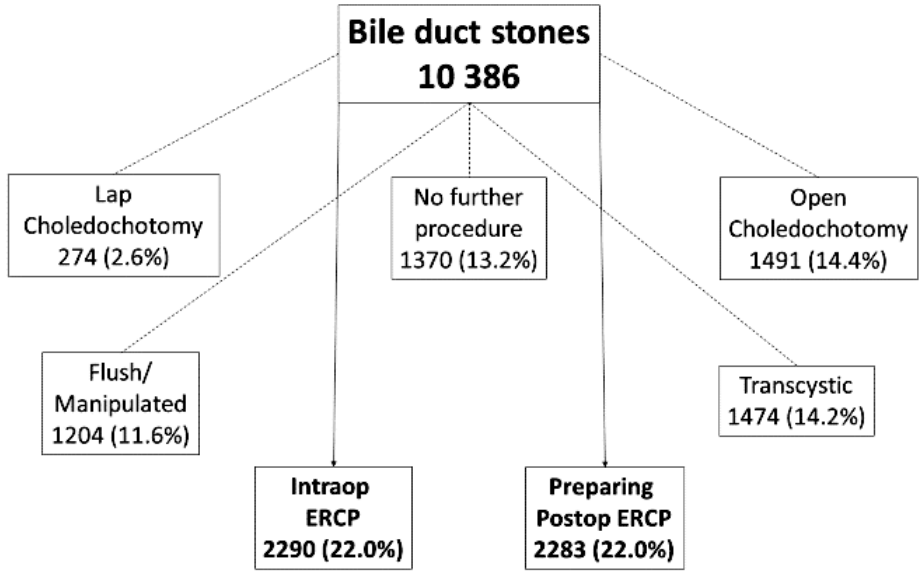


Figure 22. Flowchart common bile duct stones in Sweden 2006–2016.

Paper III

Paper III was based on data from procedures for gallstone disease registered in the Swedish Register for Cholecystectomy and ERCP (GallRiks) 2006–2014. ERCP and cholecystectomy procedures performed for confirmed or suspected CBDS were included.

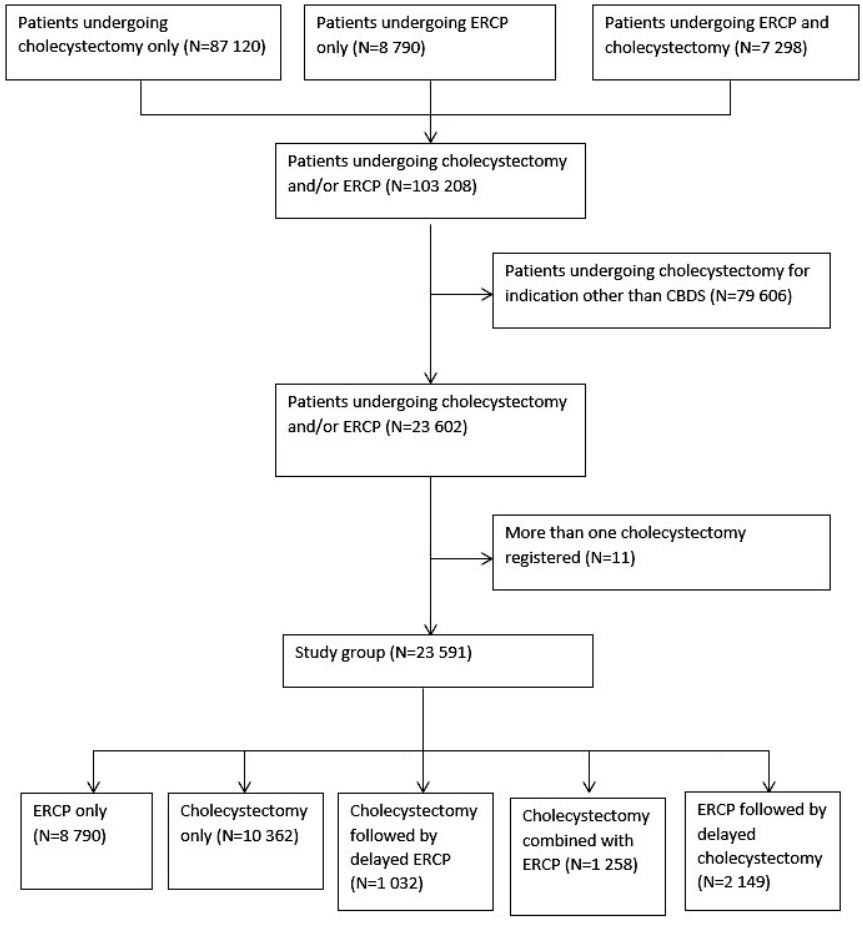


Figure 23. Flow chart. Confirmed or suspected CBDS as indication for treatment.

Patients with confirmed or suspected CBDS were divided into five treatment groups: ERCP only; cholecystectomy only; cholecystectomy followed by delayed ERCP; cholecystectomy combined with ERCP; or ERCP followed by delayed cholecystectomy.

Postoperative events were registered by cross-matching GallRiks with the National Patient Register (NPR). A postoperative cardiovascular event was defined as an ICD-code in the discharge notes indicating myocardial infarct,

pulmonary embolism, or cerebrovascular incident within 30 days after surgery. In cases where a patient had undergone ERCP and cholecystectomy on separate occasions, the 30-day interval was timed from the first intervention.

Paper IV

Data from GallRiks on all ERCPs 2009-2018 performed for common bile duct stone (n=17873) and malignancy (n=6152), with complete registration and 30-day follow-up, were collected and compiled. Procedures for any other indication, procedures on patients having undergone previous ERCP since 2006, and rendezvous ERCPs were excluded from the analysis. Associations between

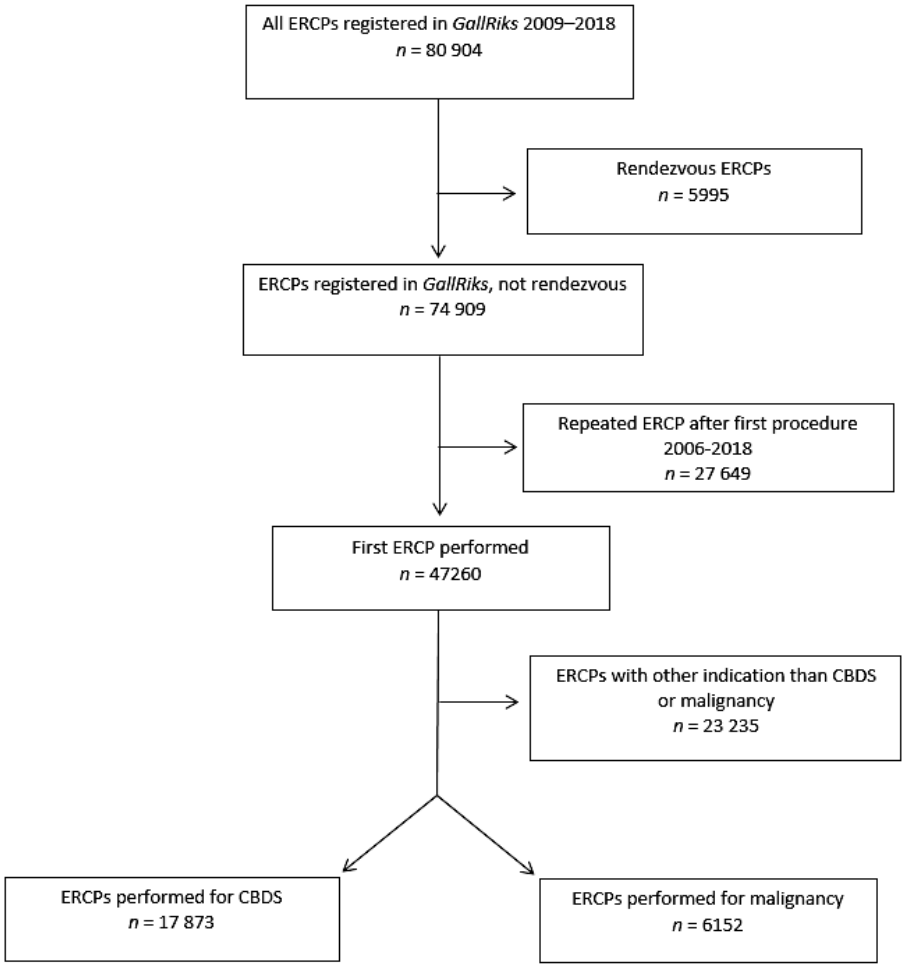


Figure 24. Flow chart showing study group assembly.

endoscopist ERCP case-volume as well as centre case-volume and successful cannulation rate, procedure time, intraoperative complication rate, and post-operative complication rate within 30 days (PEP, perforation, and intra- and postoperative bleeding) were analysed. Case-volumes were based on those during the year preceding the observations. When calculating cumulative volume of ERCP procedures for endoscopists and centres, no ERCPs were excluded.

Statistical Analyses

Paper I

Univariable and multivariable logistic regression analyses with PEP as endpoint were undertaken. In the multivariable analyses, adjustment was made for sex and age (at least 65 years versus less than 65 years) based on assumptions of cause-effect relationships.

A subgroup analysis was conducted on patients with a previous history of pancreatitis. In this subgroup analysis the mean time that had elapsed since the previous episode of pancreatitis and ERCP was compared between patients who developed PEP following ERCP and those who did not suffer this complication, using Student's t test.

Paper II

Univariate and multivariate regression analyses were used as well as Pearson Chi Square Test and Student's T-Test. The analyses were based on patients undergoing cholecystectomy with intraoperative ERCP, and patients undergoing cholecystectomy as well as postoperative ERCP in two separate procedures. The complication rate was determined by extracting intraoperative and postoperative complications within 30 days after the cholecystectomy as well as the postoperative ERCP. In univariate and multivariate logistic regression analyses, the odds ratio for intra- and postoperative complications was determined, adjusted for gender, age and ASA score. Statistical significance was defined as $p<0.05$.

Paper III

To adjust for confounders, multivariate logistic regression analyses were performed, with cardiovascular event (myocardial infarct and/or pulmonary embolus and/or cerebrovascular incident), and death within 30 days as endpoints. The multivariate models were based on age (≥80 years vs <80 years), ASA class (III-V vs I-II), gender, treatment, and history of cardiovascular condition or event (myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular incident, diabetes with secondary complication, or pulmonary

embolism). Patients who underwent cholecystectomy and ERCP during the same operation and those who underwent cholecystectomy and delayed ERCP were grouped together with the cholecystectomy group, whereas those who underwent ERCP and delayed cholecystectomy were grouped together with the ERCP group. This grouping was based on the intervention primarily intended to manage the CBDS. Poisson regression was used to calculate the 30-day age- and gender-adjusted standardised mortality ratio (SMR) based on the expected mortality rate extrapolated from the Swedish general population in 2007.

Paper IV

Univariable and multivariable logistic regression analyses with successful cannulation, procedure time, intraoperative complication rate, and postoperative complication rate within 30 days (PEP, perforation, and intra- and postoperative bleeding) as endpoints were carried out with endoscopist- and centre case-volumes as exposure variables. In the multivariable logistic regression analyses, adjustments were made for gender, age, and year of ERCP. The adjustments made in the multivariable analysis were based on assumptions of cause-effect relationships. Analyses were made with case-volumes on a log scale (n=0-4, 5-10, 11-20, 21-40, 41-80, 81-160 or 161-320 for endoscopist and n=0-20, 21-40, 41-80, 81-160, 161-320 or >320 for centre).

Ethical Considerations

Paper I

The Regional Ethics Review Board in Stockholm approved the study the 18th March 2015 (reference number 2015/339-31/1).

Paper II

The Regional Ethics Review Board in Uppsala approved the study the 2nd November 2016 (reference number: 2016/281/1).

Paper III

The Regional Ethics Review Board in Stockholm approved the study the18th March 2015 (IRB-approval, reference number: 2015/339-31/1).

Paper IV

The Regional Ethics Review Board in Stockholm approved the study the 17th June 2020 (IRB-approval, reference number: 2020-01450).

Results

Paper I

Women (Odds Ratio [OR] 1.33, 95% confidence interval [CI] 1.14-1.55), patients aged less than 65 years (OR 1.68, CI 1.45-1.94), patients with hyperlipidaemia (OR 1.32, CI 1.02-1.70), and those with a previous history of acute pancreatitis (OR 5.44, CI 4.68- 6.31) faced a significantly higher risk for PEP. In a subgroup analysis of patients with a previous history of acute pancreatitis, the mean time from previous pancreatitis to ERCP was 4423 days in patients who developed PEP versus 6990 days in patients who did not (P =0.037). However, when the previous episode of pancreatitis had occurred more than 30 days before ERCP, this association was no longer significant (P =0.858). Patients with diabetes had a lower risk for PEP (OR 0.64, CI 0.48-0.85).

Table 6. Univariable and multivariable logistic analysis of risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography. Adjustments were made for sex and age (at least 65 years versus less than 65 years).

	Incidence of post-ERCP pancreatitis	Univariable analysis Odds ratio	p	Multivariable analysis Odds ratio	p
Gender					
Men	250/6140 (4.1%)				
Women	515/9660 (5.3%)	1.33 (1.14-1.55)	<0.001		
Age					
≥65 years	349/9140 (3.8%)				
<65 years	416/6660 (6.2%)	1.68 (1.45-1.94)	<0.001		
History of acute pancreatitis	363/2567 (14.1%)	5.26 (4.53-6.10)	<0.001	5.44 (4.68-6.31)	<0.001
Diabetes (all)	56/1947 (2.9%)	0.55 (0.42-0.72)	<0.001	0.64 (0.48-0.85)	0.002
Diabetes type 1	21/564 (3.6%)	0.72 (0.47-1.13)	0.724	0.84 (0.54-1.31)	0.437
Liver cirrhosis	12/185 (6.5%)	1.37 (0.76-2.47)	0.296	1.39 (0.77-2.51)	0.277
Hyperlipidaemia	72/1394 (5.2%)	1.08 (0.84-1.38)	0.556	1.32 (1.02-1.70)	0.036
Hypercalcaemia	2/58 (3.4%)	0.70 (0.17-2.88)	0.622	0.76 (0.18-3.11)	0.756
Kidney disease	27/579 (4.7%)	0.96 (0.65-1.42)	0.838	1.16 (0.78-1.72)	0.474

Paper II

Intraoperative ERCP increased (7.5% 2006; 43.1% 2016) whereas preparation for postoperative ERCP decreased (21.2% 2006; 17.2% 2016) 2006-2016. CBDS management differed between TRHs and CHs. Complications were higher in the postoperative rendezvous ERCP group: (Odds Ratio [OR] 1.69, 95% confidence interval [CI] 1.16-2.45) for intraoperative complications and (OR 1.50, CI 1.29-1.75) for postoperative complications. The risks for intraoperative bleeding (OR 2.46, CI 1.17-5.16), postoperative bile leakage (OR 1.89, CI 1.23-2.90), and postoperative infection with abscess (OR 1.55, CI 1.05-2.29) were higher in the postoperative group. Post-ERCP pancreatitis, postoperative bleeding, cholangitis, percutaneous drainage, antibiotic treatment, ICU stay, readmission/reoperation within 30 days, and 30-day mortality did not differ between groups.

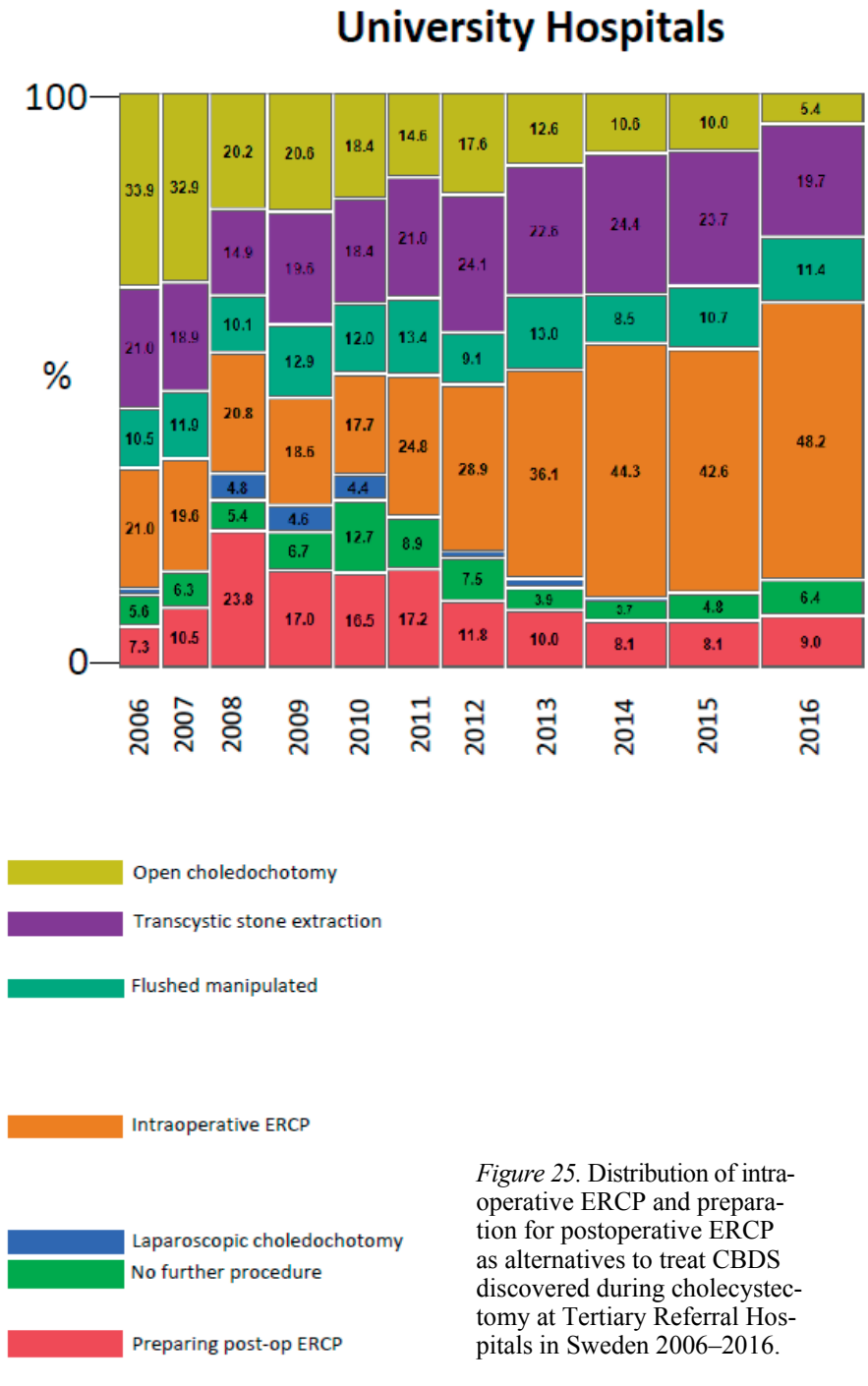


Figure 25. Distribution of intraoperative ERCP and preparation for postoperative ERCP as alternatives to treat CBDS discovered during cholecystectomy at Tertiary Referral Hospitals in Sweden 2006–2016.

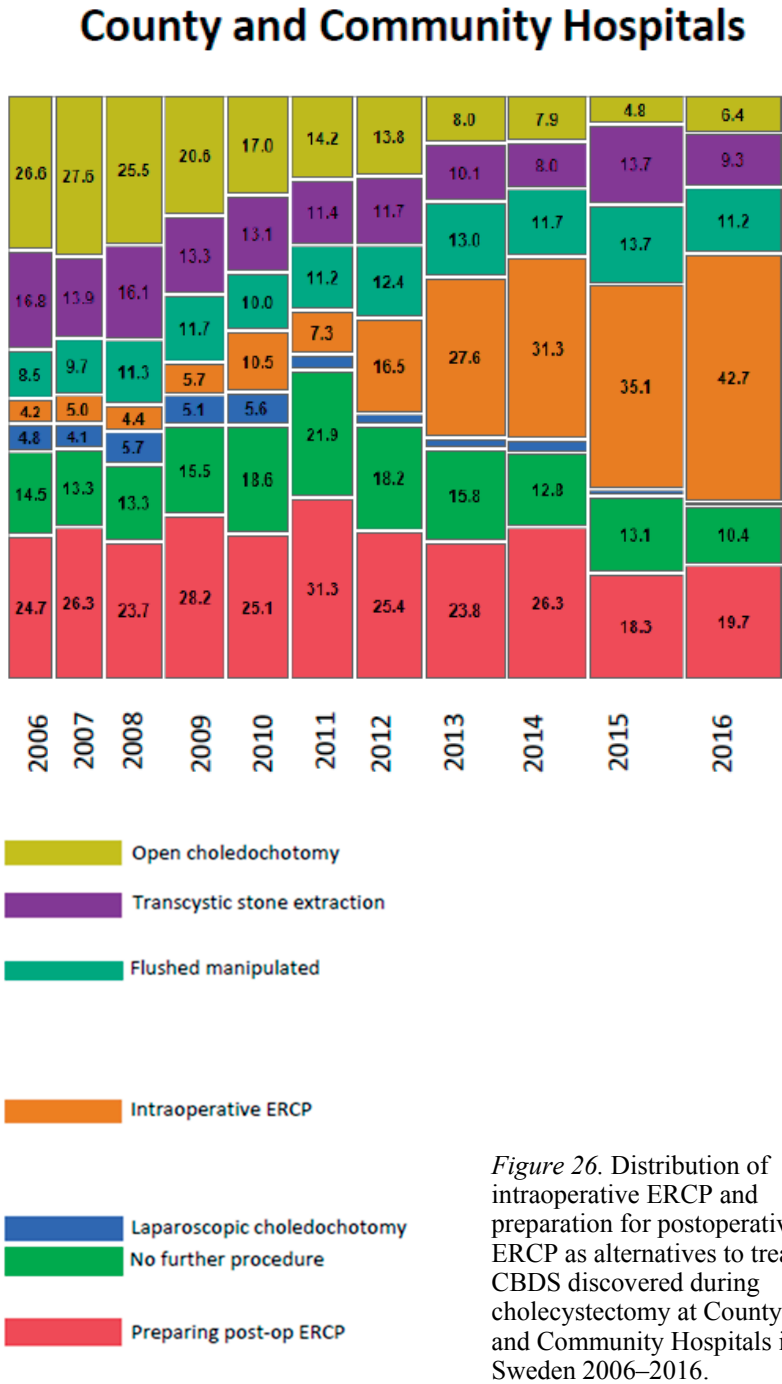


Figure 26. Distribution of intraoperative ERCP and preparation for postoperative ERCP as alternatives to treat CBDS discovered during cholecystectomy at County and Community Hospitals in Sweden 2006–2016.

Table 7. Intra- and postoperative (within 30 days) complication rates n (%). Statistically significant values are given in bold text. Pearson Chi Square.

		Intraop ERCP (%)	**Preparation postop ERCP (%)**	***P****
Intraoperative	Overall	2.0	3.4	**0.0031**
	Bleeding	0.4	1.1	**0.0106**
Postoperative	Overall	15.6	21.8	**<0.0001**
	Bleeding	1.2	0.9	0.2501
	Pancreatitis	4.7	4.4	0.6362
	Cholangitis	0.6	0.9	0.2314
	Bile leakage	1.4	2.7	**0.0025**
	Infection with abscess	1.9	2.9	**0.0197**
	Percutaneous drainage	2.2	3.0	0.0925
	Antibiotic treatment	9.7	10.4	0.4697
	ICU stay	0.3	0.1	0.3191
	Readmission within 30 days	0.7	0.3	**0.0498**
	Reop within 30 days	2.0	2.1	0.8232
	Mortality 30 days	0.31	0.04	**0.0341**

Table 8. Multivariate analysis with intra- and postoperative complications as outcome measures and preparation for postoperative versus intraoperative ERCP as exposures, adjusting for gender, age, and ASA class. Statistically significant OR are given in bold text.

		Intraop ERCP ref		
		OR	**95% CI**	***P***
Intraoperative	Overall	1.69	(1.16-2.45)	**0.0061**
	Bleeding	2.46	(1.17-5.16)	**0.0170**
Postoperative	Overall	1.50	(1.29-1.75)	**<0.0001**
	Bleeding	0.72	(0.40-1.28)	0.2581
	Pancreatitis	0.95	(0.72-1.25)	0.7053
	Cholangitis	1.53	(0.77-3.02)	0.2229
	Bile leakage	1.89	(1.23-2.90)	**0.0034**
	Infection with abscess	1.55	(1.05-2.29)	**0.0270**
	Percutaneous drainage	1.34	(0.93-1.94)	0.1191
	Antibiotic treatment	1.06	(0.88-1.29)	0.5336
	ICU stay	0.51	(0.13-2.04)	0.3394
	Readmission within 30 days	0.41	(0.16-1.07)	0.0681
	Reop within 30 days	1.05	(0.70-1.58)	0.8146
	Mortality 30 days	0.16	(0.02-1.35)	0.0927

Paper III

A total of 23 591 patients underwent ERCP or cholecystectomy for CBDS during the study period. A postoperative cardiovascular event was registered in 164 patients, and death within 30 days in 225 patients. In the univariable analysis, adverse cardiovascular event and death within 30 days were more frequent in patients who underwent primary ERCP ($p<0.05$). In the multivariable analysis adjusting for history of cardiovascular disease or events, neither risk for cardiovascular complication nor death within 30 days remained statistically significant in the ERCP group.

Table 9. Postoperative adverse events in confirmed or suspected CBDS within 30 days in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangio-pancreatography (GallRiks) 2006–2014.

	ERCP only (N=8 790)	Cholecyst-ectomy only (N=10 362)	Cholecyst-ectomy followed by delayed ERCP (N=1 032)	Cholecyst-ectomy combined with ERCP (N=1 258)	ERCP followed by delayed cholecyst-ectomy (N=2 149)	Total com plication (N=164) and death (N=225)
Myocardial infarct	62 (0.71%)	13 (0.13%)	3 (0.29%)	1 (0.08%)	3 (0.14%)	82
Cerebro-vascular lesion	23 (0.26%)	5 (0.05%)	1 (0.10%)	0 (0%)	2 (0.09%)	31
Pulmonary embolism	23 (0.26%)	19 (0.18%)	4 (0.39%)	3 (0.24%)	2 (0.09%)	51
Postoperative death	173 (1.97%)	43 (0.41%)	4 (0.39%)	3 (0.24%)	2 (0.09%)	225

Table 10. Univariable and multivariable analyses of factors predicting cardiovascular event and death within 30 days after surgical and/or endoscopic treatment for confirmed or suspected CBDS in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography (GallRiks) 2006–2014.

Univariable				
	Cardiovascular complication		Death	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Age≥80 years (ref <80 years)	4.37 (3.20-5.60)	<0.001	9.60 (7.20-12.79)	<0.001
Men (ref women)	1.16 (0.85-1.59)	0.340	1.19 (0.91-1.55)	0.197
ASA I (ref)				
ASA II	3.83 (2.16-6.79)	<0.001	6.42 (3.08-13.35)	<0.001
ASA III	9.82 (5.51-17.52)	<0.001	31.39 (15.32-64.31)	<0.001
ASA IV	26.03 (11.44-59.22)	<0.001	150.02 (67.94-331.23)	<0.001
ASA V	-	-	343.38 (32.20-3662.14)	<0.001
History of cardiovascular disease or event*	10.20 (7.12-14.60)	<0.001	6.25 (4.74-8.23)	<0.001
ERCP (ref cholecystectomy)**	2.74 (1.95-3.84)	<0.001	4.10 (3.00-5.62)	<0.001
Multivariable				
	Cardiovascular complication		Death	
ERCP (ref cholecystectomy)*	1.12 (0.77-1.64)	0.548	1.38 (0.97-1.96)	0.071

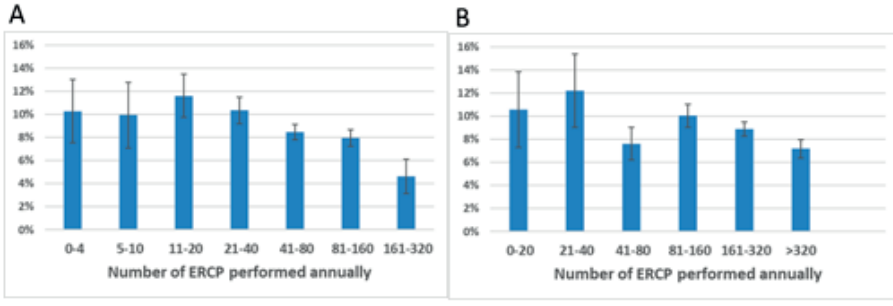
** History of myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular incident, diabetes with secondary complication, or pulmonary embolism.*

***In cases where ERCP as well as cholecystectomy were performed, the procedures were grouped according to the primary procedure. If cholecystectomy and ERCP were performed as one procedure, the procedure was included in the cholecystectomy group.*

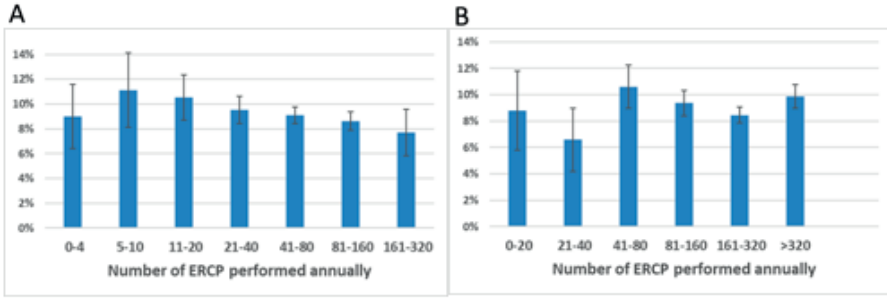
Paper IV

In the multivariable analysis of the CBDS group adjusting for age, gender and year, a high endoscopist case-volume was associated with higher successful cannulation rate with lower complication and PEP rates and shorter procedure time ($p<0.05$). High annual case-volume centres were associated with high successful cannulation rate and shorter procedure time ($p<0.05$), but not lower complication and PEP rates.

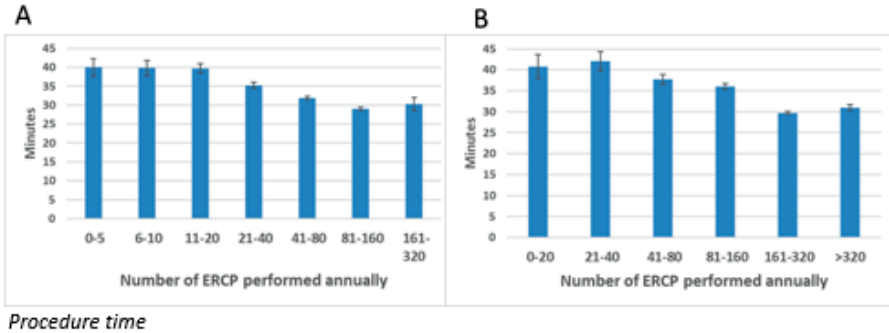
When indication for ERCP was malignancy, a high endoscopist case-volume was associated with high successful cannulation rate and low PEP rates ($p<0.05$), but not shorter procedure time or lower complication rate. Centres with high case-volume were associated with high successful cannulation rate and low complication and PEP rates ($p<0.05$), but not shorter procedure time.



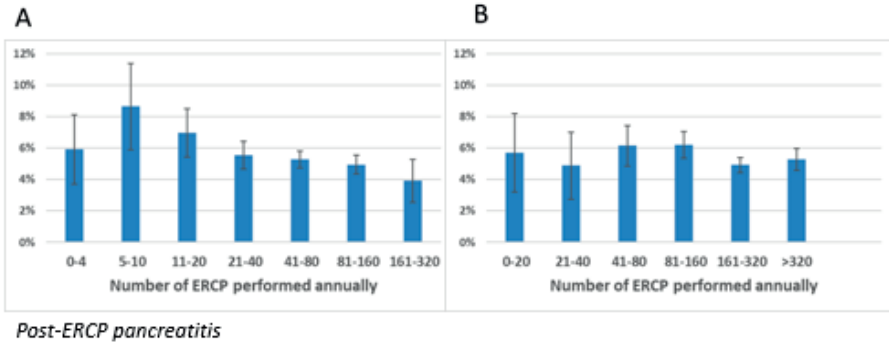
Unsuccessful deep cannulation of bile duct



Intra- and postperative complications within 30 days

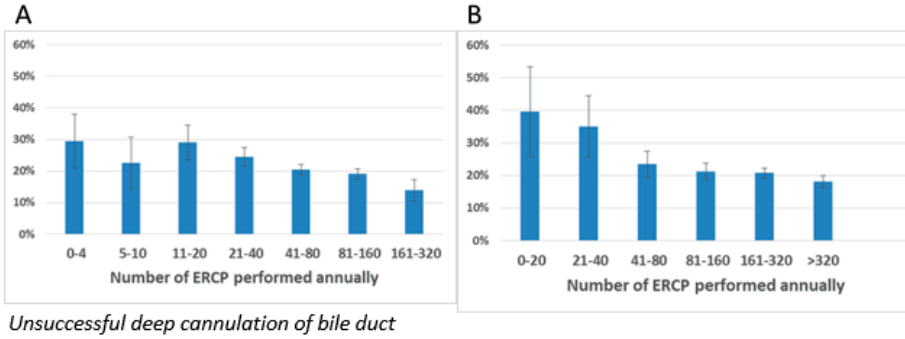


Procedure time

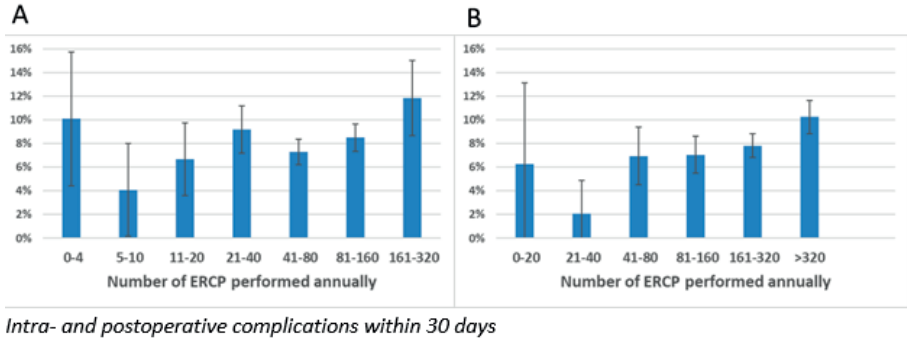


Post-ERCP pancreatitis

Figure 27. ERCPs 2009-2018 with indication common bile duct stone. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct (in this figure illustrated as unsuccessful deep cannulation), intra- and postoperative complications within 30 days and post-ERCP pancreatitis (P EP) as outcome. A=Endoscopist, B=Centre



Unsuccessful deep cannulation of bile duct



Intra- and postoperative complications within 30 days

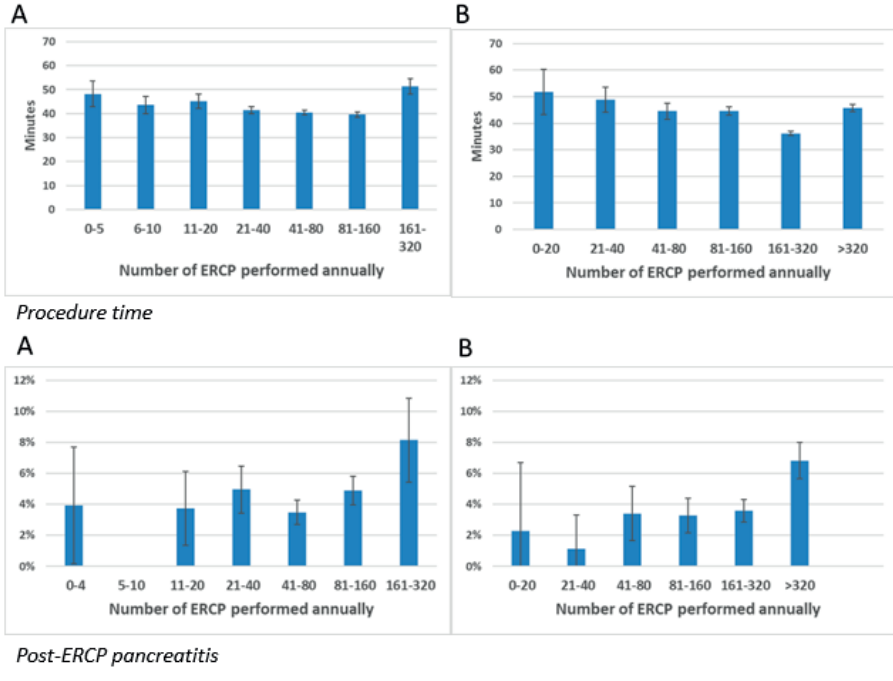


Figure 28. ERCPs 2009-2018 with indication malignancy. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct (in this figure illustrated as unsuccessful deep cannulation), intra- and postoperative complications within 30 days and post-ERCP pancreatitis (PEP) as outcome. A=Endoscopist, B=Centre

Discussion

The results of the studies in this thesis may serve to identify patients and situations where there is an increased risk for ERCP-related complications. Even if procedure-related complications cannot be eliminated, awareness of potential risk factors may help to optimise safety in situations where problems are foreseen. When hazards and risk factors are identified, the care of patients with gallstone disease can be organised to prevent them.

The prevalence of gallstone-related symptoms, including CBDS, in the population is 7-15%. Choledocholithiasis is the most common indication for ERCP, about 3 times more common than malignancy as indication, and procedures for CBDS are performed at almost all hospitals in Sweden where gallstone surgery is carried out [9, 185]. High age is a significant risk factor for prolonged hospital stay and for death after any procedure for gallstone removal [81, 82]. The comorbidity rate in elderly patients undergoing treatment for choledocholithiasis is high compared to younger patients, and there is a tendency to choose minimally-invasive treatment methods such as ERCP when it comes to older, frail patients with high comorbidity [83, 88]. ERCP performed for CBDS may be complicated, for example large impacted stones that require advanced methods such as electrohydraulic lithotripsy (EHL). The majority of ERCPs for CBDS, however, are uncomplicated and fall into H.O.U.S.E. category I [33], Cotton Grade II, or Schutz II [31, 32]. ERCP for the diagnosis and treatment of malignancy is often more complicated than ERCP for CBDS, especially if the malignancy is intrahepatic. These procedures are associated with greater risk and higher adverse event rates. ERCP for malignancy is graded at least H.O.U.S.E. II, Cotton III, or Schutz IV [31-33].

The reported complication rate of ERCP is 10-15%. The most common adverse event is post-ERCP pancreatitis (PEP), with a rate of 3.5-5% [9, 51, 52]. The risk for ERCP complications depends on both patient risk factors and technical risk factors related to the procedure and experience of the endoscopist and team [8, 9, 43, 49, 50]. High endoscopist- and centre ERCP case-volumes have been shown to be correlated to high success rates in terms of successful cannulation and fewer adverse events [30, 57, 172-176].

In the case of CBDS found at IOC, the frequency of open choledochotomy, once considered the first-hand technique, has decreased in recent years, while at the same time, minimally invasive laparoscopic and laparo-endoscopic methods, mainly intraoperative rendezvous ERCP, have come to predominate

[9, 10, 14, 18, 20, 21, 24-29]. ERCP has traditionally been performed as a two-stage procedure, either as preoperative ERCP followed by laparoscopic cholecystectomy or laparoscopic cholecystectomy followed by postoperative ERCP. However, 4–18% of attempted ERCPs are interrupted due to inability to cannulate the bile duct. ERCP may also lead to serious complications such as PEP [9, 44, 51].

The technique of intraoperative rendezvous ERCP is straight-forward and suitable for almost all patients with CBDS. In this way cholecystectomy and management of CBDS are performed at the same time, thereby limiting anaesthesia to one procedure with minimal hospital stay, healthcare resources, and costs [36-43]. Even if intraoperative rendezvous ERCP is recommended as method of choice, postoperative rendezvous ERCP is an alternative to intraoperative ERCP in situations when ERCP resources are limited [14, 46-48]. As the lack of uniform logistic routines has made it impossible to conduct a prospective randomised controlled trial comparing the two methods, the best evidence regarding the safety and effectiveness of the two approaches has been derived from large population-based studies.

In Papers I and III we focused on risk factors for PEP and cardiovascular complications and death after surgical treatment for CBDS. In accordance with previous studies, we found that women, patients aged less than 65 years, and those with a previous history of acute pancreatitis had a significantly greater risk for developing PEP [49-51, 54, 55]. Since it is difficult to distinguish a new episode of acute pancreatitis from an exacerbation of an ongoing process, we excluded patients with pancreatitis immediately before ERCP. This showed that if the previous episode of pancreatitis occurred more than 30 days before the ERCP, the time factor was not associated with risk for PEP. As shown in previous studies, hypertriglyceridaemia and hyperlipidaemia both increase the risk for PEP while liver cirrhosis is not a risk factor [58, 59, 62, 68].

Associated comorbidities such as obesity, alcohol abuse and use of medications were not investigated in the present study since these data were not available in GallRiks.

Although previous reports give contrasting results with respect to hypercalcaemia/kidney disease and risk for PEP [60, 61, 64], it should be noted that only 58 patients in the present cohort had hypercalcaemia and 579 had kidney disease. With no data on the degree of renal failure it is difficult to draw any conclusion regarding the association between hypercalcaemia/kidney disease and PEP.

Whereas previous studies have shown diabetes to be associated with acute pancreatitis [65, 67], we paradoxically found a lower risk for PEP in patients with diabetes. It has been observed that the risk for acute pancreatitis is dependent on the type of diabetes medication the patient receives [63]. The cohort in the present study included diabetic patients on different kinds of diabetic treatment, and the register lacked information on disease severity and

treatment. Thus, associations between type of diabetes treatment and PEP were not investigated.

The five CBDS treatment groups in Paper III were not predetermined, and the treatments used depended on several factors such as complexity and state of the biliary disease and preference of the surgeon responsible or local treatment guidelines [191]. We believe that the choice of ERCP in patients that are frail and have greater comorbidity explains why ERCP was significant in univariate analysis. In multivariable analysis, however, adjusting for history of cardiovascular disease or events, neither risk for cardiovascular complication nor death within 30 days remained statistically significant in the ERCP group.

No subsequent cholecystectomy was registered for any of the 8790 patients with ERCP as sole intervention. It is possible, however, that some of the patients underwent cholecystectomy after completion of the study. Since cholecystectomy at a later stage was unlikely to be performed to prevent CBDS, such cases are irrelevant in the present study.

Regarding Paper III, it is possible that procedure-related complications predisposed to cardiovascular complications. This must also be taken into account when deciding on method of treatment for common bile duct stones. Even if most complications are included, it cannot be excluded that registration of some adverse events might have been neglected in the analysis of patients who underwent both ERCP and cholecystectomy on two separate occasions with a long interval between.

Tobacco use and obesity are major risk factors that must be taken into account when assesing the risk for cardiovascular complications following a surgical or endoscopic intervention. Even if smoking and BMI are included in the ASA physical status, these risk factors per se were not routinely registered in GallRiks during the period of the study, and data on medications, including anticoagulation, were lacking [192]. Anaesthesia was not included as risk factor in the present study, though this was explored in a recent study based on GallRiks data, showing more postoperative complications after ERCPs performed under deep sedation compared to those performed under general anaesthesia [193].

The burden of cardiovascular disease differs between Sweden and other parts of the world. U.S. and Swedish data are more similar than when comparing western countries with areas outside Western Europe and North America [194].

In Paper II we looked at how the management of CBDS found at IOC has changed over time as well as differences in choice of treatment between tertiary referral hospitals and smaller community/county hospitals. We focused on the two most common treatment options for choledocholithiasis i.e., intraoperative and postoperative rendezvous ERCP, and compared these methods regarding intraoperative and postoperative complication rates as well as readmission, reoperation, and mortality.

During the period 2006-2016, ERCP gradually became the method of choice to manage CBDS at all hospitals in Sweden, and by 2016 was used in 60% of procedures. Though intraoperative rendezvous ERCP was the method of choice at most hospitals, it was mostly used in TRHs. On the other hand, in 2016, preparation for postoperative rendezvous ERCP was performed twice as often in CHs than in TRHs, probably due to lack of endoscopy resources for performing intraoperative ERCP in non-specialised centres.

Intraoperative complication rates as well as rates within 30 days after the procedure were assessed and compared between intraoperative ERCP and preparation for postoperative ERCP. Since intraoperative ERCP is carried out during cholecystectomy and postoperative ERCP is usually performed within 1 or 2 days after cholecystectomy, it cannot be excluded that some of the complications observed could have been the result of cholecystectomy rather than the ERCP.

Overall intra- and postoperative complication rates, as well as intraoperative bleeding, postoperative bile leakage and postoperative infection with abscess were higher with postoperative rendezvous ERCP compared to intraoperative rendezvous ERCP. Manipulation of the guidewire while preparing for postoperative ERCP could be one possible explanation for the higher rate of postoperative bile leakage and infection in this group. If the clips around the cystic duct anchoring the guide wire are applied too loosely, the risk for subsequent bile leakage is considerable.

The rate of the most common surgical complication, PEP, as well as postoperative bleeding, cholangitis, need for percutaneous drainage, antibiotic treatment, ICU stay, readmission/reoperation within 30 days, and 30-day mortality did not differ between intraoperative and postoperative ERCP. Preparation for postoperative rendezvous ERCP by leaving a guidewire for definitive treatment of CBDS 1-2 days after cholecystectomy, is thus a feasible alternative. The routine of leaving a guidewire through the abdominal wall and taped to the skin causes some discomfort for the patient, though most seem to tolerate the guidewire quite well.

Based on the results of this study we believe that postoperative rendezvous ERCP is an acceptable alternative to intraoperative rendezvous ERCP when adequate ERCP resources are lacking or limited.

In Paper IV it was demonstrated that case-volume of the endoscopist has a great impact on ERCP outcome, especially when performed for CBDS. The pattern was more obscure for procedures performed for suspected malignancy. At the centre level, annual case-volume was also associated with safer outcome.

To obtain a more homogenous study population, we excluded all procedures where the indication was unclear, which to some extent limits the external validity of the study. Registration of incorrect indication and incomplete-

ness and low frequency of 30-day follow-up affect results and outcome. Regarding complicated ERCP procedures, postoperative complication rates have been shown to be higher in units where follow-up is complete

[195]. GallRiks has not yet been linked to the Swedish National Patient Register (NPR), so some complications, particularly those occurring after 30 days, may have been neglected. However, it is more likely that most adverse events following ERCP occur in the immediate postoperative period.

Since perioperative complication rates, in particular PEP, are low, we chose to exclude rendezvous ERCPs [36, 41]. Endoscopists with the greatest experience and centres with the highest volumes had the highest cannulation success rate, shortest procedure times, and lowest complication rates when the indication for ERCP was CBDS. Paradoxically, the outcome of ERCP performed for malignancy by more experienced endoscopists was poorer, with longer procedure times and higher complication rates. This was probably the result of selection bias since the most experienced high-volume endoscopist performs the most complex and time-consuming ERCP procedures with the greatest risk for adverse events. This results in residual confounding, which was not captured in the analyses of the present study. Furthermore, high-volume endoscopists use more advanced ERCP techniques such as needle-knife sphincterotomy, and are more likely to persevere longer and spend greater effort cannulating the bile duct before terminating the procedure [196].

Case-volume is an important issue in ERCP training, and it is important that the training of future advanced endoscopists is carried out at high-volume centres. The learning curve among trainees in advanced endoscopy varies significantly, but the success rate of trainees performing ERCP increases with experience [197, 198].

Conclusions

Paper I

Age, female gender, hyperlipidaemia, and previous history of recent acute pancreatitis increase the risk for PEP. Diabetes, however, appeared to lower the risk for PEP.

Paper II

The choice of technique for management of CBDS found at cholecystectomy has changed in recent years and differs between TRHs and CHs. Rendezvous ERCP is now the technique of choice and is performed at practically all hospitals in Sweden.

Rendezvous ERCP is a safe and effective method. Intraoperative rendezvous ERCP is to be preferred, but postoperative rendezvous ERCP is a perfectly acceptable alternative when adequate ERCP resources are lacking or limited.

Paper III

Primary ERCP as well as cholecystectomy may be performed for CBDS with acceptable safety. More studies are required to provide reliable guidelines for the management of CBDS.

Paper IV

The results of Study IV suggest that higher endoscopist- and centre case-volumes lead to safer and more effective ERCPs.

Proposals for future clinical research

- Prospective randomised studies are required to clarify the potential protective effect of NSAID regarding PEP. Since the results of previously published prospective randomised controlled studies are contradictory, recommendations concerning PEP prophylaxis in Sweden differ and most ERCP patients are not given NSAID [9, 51, 153, 165]. We are therefore planning a nationwide multicentre study comparing the frequency and severity of PEP, according to Cotton's criteria, between patients randomised to receive100 mg diclofenac administered rectally immediately prior to ERCP and those with no prophylaxis. Adverse event and mortality rates will also be analysed.

  The Regional Ethics Review Board in Uppsala approved the study the 31st May, 2017 (reference number: 2017/067).

  The Medical Products Agency approved the study the 20th August, 2018 (reference number: 5.1-2018-56693, EU-number: 2017-004250-42).

- A supplementary research study would be to retrieve GallRiks data regarding ERCP patients who received prophylactic rectally administered NSAID and compare their intra- and postoperative complication rates with patients who were not premedicated with NSAID.

- Another option would be to compare complication and success rates in patients undergoing ERCP who have been treated with early precut sphincterotomy with those who have been treated with regular sphincterotomy.

Summary of the thesis in Swedish

Bakgrund

Endoskopisk Retrograd Kolangiopankreatografi (ERCP) är en endoskopisk röntgenbaserad behandlingsmetod för att utreda och behandla sjukdomstillstånd i gallvägar och i bukspottkörtel. Årligen utförs drygt 9000 ERCP i Sverige och den vanligaste indikationen är sten i djupa gallvägarna följt av tumörorsakad gallvägsförträngning. Den totala komplikationsfrekvensen efter ERCP uppgår till 10-15%. Risken för komplikation beror både på patient- och procedurrelaterade faktorer liksom på endoskopistens och teamets erfarenhet och undersökningsvolym. Den vanligaste komplikationen utgörs av bukspottkörtelinflammation, post-ERCP pankreatit (PEP), vilken drabbar 3.5-5% av patienter. PEP definieras som buksmärtor>24 timmar samt s-amylas (bukspottkörtelenzym i blodet) >3 gånger normalvärdet tillika med förlängd vårdtid eller återinläggning på sjukhus. Inflammationen i bukspottkörteln blir i de allra flesta fall lätt till måttlig och läker inom några dagar men kan ibland bli allvarlig och kräva intensivvård eller, i sällsynta fall, till och med leda till döden. Exempel på riskfaktorer för PEP är långvarig manipulation av gallgångsmynningen, ingjutning av röntgenkontrast i bukspottkörtelgången, ung ålder och kvinnligt kön.

Livstidsrisken att utveckla gallsten är >20% och av personer med gallsten drabbas 10-20% av stensjukdom i djupa gallvägarna med risk för allvarliga komplikationer som obstruktiv gulsot, gallvägsrelaterad infektion (kolangit) eller bukspottkörtelinflammation (pankreatit). Riskfaktorer för att utveckla gallsten inkluderar hög ålder, kvinnligt kön, graviditet, fysisk inaktivitet och fetma. Att operera bort gallblåsan med titthålsteknik (laparoskopisk kolecystektomi) är förstahandsbehandling för gallsten runt om i världen och enbart i Sverige utförs 13 000 kolecystektomier årligen. Intraoperativ röntgen av gallvägarna (kolangiografi) har visats vara effektiv för att klargöra gallvägsanatomin samt detektera sten i djupa gallvägarna, vilket sker i 10-15% av kolecystektomier. Den vanligaste metoden i vårt land att åtgärda sten i djupa gallvägarna som upptäcks under pågående galloperation är peroperativ rendezvous ERCP. Med denna teknik underlättas accessen till de djupa gallvägarna med hjälp av en ledare (guidewire) som under röntgengenomlysning förs via ytliga gallgången till tolvfingertarmen. Peroperativ rendezvous ERCP har, jämfört med konventionell icke-rendezvous ERCP, visats ge hög grad av stenfrihet och minskad risk för komplikationer, framför allt PEP. I situationer

där tillgång till endoskopisk expertis saknas kan ett alternativ vara att förankra ledaren via ytliga gallgången till tolvfingertarmen, avsluta kolecystektomin och utföra ERCP i en andra seans, så kallad postoperativ rendezvous ERCP. Hos vissa äldre och sköra patienter där komplikationsrisken vid kirurgi bedöms alltför hög kan ERCP med stenextraktion utgöra den enda behandlingen vid sten i djupa gallvägarna.

Delarbetena i denna avhandling utgår från data från det svenska kvalitetsregistret för gallstenskirurgi och ERCP (GallRiks). GallRiks startade 2005 och omfattar >90% av alla kolecystektomier och ERCP:er i Sverige. Patient- och procedurrelaterade data förs in på förhand och intra- och postoperativa komplikationer inom 30 dagar registreras lokalt av koordinator på varje sjukhus/enhet.

Delarbete I

Syftet med detta arbete var att undersöka huruvida vissa förutbestämda parametrar och sjukdomstillstånd påverkar risken att drabbas av post-ERCP pankreatit. De parametrar/tillstånd som undersöktes var ålder, kön ASA klass (riskklass I-IV utifrån tidigare sjuklighet och funktionsnivå), tidigare akut pankreatit, diabetes, hyperlipidemi (höga blodfetter), hyperkalcemi (förhöjt kalcium), njursjukdom och levercirrhos (skrumplever). 15 800 ERCP:er som utförts 2006-2014 på indikation sten i djupa gallvägarna analyserades och data samkördes med nationella patientregistret. Patienter <65 år, kvinnor, patienter med höga blodfetter och de som nyligen haft pankreatit hade en ökad risk för bukspottkörtelinflammation efter ERCP medan patienter med diabetes uppvisade en lägre risk.

Delarbete II

I detta arbete studerades hur frekvensen av olika tekniker för att behandla sten i djupa gallvägarna som upptäcks under pågående galloperation har förändrats över tid på universitetssjukhus jämfört med övriga sjukhus. Vidare undersöktes om postoperativ rendezvous ERCP utgör ett säkert och effektivt alternativ till peroperativ rendezvous ERCP. Under perioden 2006-2016 registrerades 10 386 kolecystektomier där man funnit sten i djupa gallvägarna vid peroperativ röntgenundersökning. Av dessa utfördes peroperativ rendezvous ERCP i 2290 fall och förberedelse för postoperativ rendezvous ERCP skedde i 2283 fall.

Under den aktuella tidsperioden ökade andelen fall av peroperativ ERCP från 7.5% 2006 till 43.1% 2016 medan andelen fall av postoperativ ERCP minskade från 21.2% 2006 till 17.2% 2016. Metoder att hantera sten i djupa gallvägarna skilde sig åt mellan universitetssjukhus och övriga sjukhus. Den

totala komplikationsfrekvensen var högre för postoperativ ERCP jämfört med peroperativ ERCP. Vad gäller enskilda komplikationer var intraoperativ blödning, postoperativt galläckage och postoperativ infektion med abscess (inkapslad varhärd) vanligare vid postoperativ ERCP. Dock sågs ingen skillnad i komplikationsfrekvens mellan grupperna vad gäller bukspottkörtelinflammation, postoperativ blödning, infektion från gallvägarna, behov av infektionsbehandling (antibiotika, dränageslang), behov av intensivvård, återinläggning på sjukhus, reoperation eller mortalitet inom 30 dagar. Av dessa data drogs slutsatsen att postoperativ rendezvous ERCP kan utgöra andrahandsalternativ till peroperativ rendezvous ERCP i de fall ERCP resurser saknas eller är bristfälliga.

Delarbete III

Syftet med denna studie var att jämföra frekvensen av kardiovaskulära komplikationer (hjärt- kärl komplikationer) och död inom 30 dagar (hjärtinfarkt, blodpropp i lungan eller hjärninfarkt/hjärnblödning) mellan patienter som behandlats med olika metoder för sten i djupa gallvägarna. De metoder/grupper som studerades var: enbart ERCP; enbart kolecystektomi; kolecystektomi följt av ERCP; kolecystektomi tillsammans med ERCP; och ERCP följt av kolecystektomi. Data från GallRiks samkördes med nationella patientregistret.

Under perioden 2006-2014 registrerades totalt 23 591 patienter som behandlats för sten i djupa gallvägarna. Av dessa drabbades 164 patienter av kardiovaskulär komplikation inom 30 dagar och 225 patienter avled inom 30 dagar. Äldre och skörare patienter behandlades i större utsträckning med ERCP än med kolecystektomi. Efter att justering för tidigare känd kardiovaskulär sjukdom utförts sågs ingen skillnad i kardiovaskulära komplikationer eller död mellan de olika behandlingsgrupperna. Således drogs slutsatsen att kirurgi och ERCP utgör likvärdiga behandlingsmetoder för sten i djupa gallvägarna avseende risken för hjärt-kärl komplikationer. Äldre och skörare patienter behandlas i större utsträckning med ERCP än kolecystektomi.

Delarbete IV

I detta arbete undersöktes sambandet mellan ERCP-resultat och undersökningsvolym på undersökarnivå och enhetsnivå för förstagångs ERCP:

er som utförts på indikation sten i djupa gallvägarna respektive misstänkt eller känd malignitet (tumörsjukdom).

2009-2018 registrerades 17873 förstagångs ERCP:er som utförts på grund av sten i djupa gallvägarna och 6152 som utförts på indikation misstänkt eller känd malignitet, De parametrar som undersöktes och jämfördes mellan skopister och sjukhus med olika undersökningsvolym var: kanyleringsfrekvens

(andel fall där man lyckades få access till gallvägarna), undersökningstid, total intra- och postoperativ komplikationsfrekvens och frekvens bukspottkörtelinflammation.

När indikationen för ERCP var sten i djupa gallvägarna var en hög ERCP-volym hos skopisten korrelerad till högre kanyleringsfrekvens, lägre frekvens av komplikationer inklusive bukspottkörtelinflammation och kortare undersökningstid. En hög volym på enheten var korrelerad till högre kanyleringsfrekvens och kortare undersökningstid men inte till lägre frekvens komplikationer eller lägre frekvens bukspottkörtelinflammation.

När indikationen för ERCP var malignitet var hög undersökningsvolym hos skopisten kopplad till högre kanyleringsfrekvens och lägre frekvens bukspottkörtelinflammation men inte till kortare undersökningstid eller lägre total komplikationsfrekvens. Enheter med hög undersökningsvolym hade högre kanyleringsfrekvens och lägre frekvens av komplikationer och bukspottkörtelinflammation men inte kortare undersökningstid.

Dessa resultat pekar mot att högre undersökningsvolym av ERCP på skopist- och enhetsnivå är korrelerad till säkrare och mer lyckosam ERCP.

Sammanfattning

Ålder <65 år, kvinnligt kön, höga blodfetter och en nyligen genomgången bukspottkörtelinflammation ökar risken för bukspottkörtelinflammation efter ERCP medan diabetes minskar risken.

Tekniker för att behandla sten i djupa gallvägarna som upptäcks under pågående galloperation har ändrats över tid och skiljer sig mellan universitetssjukhus och övriga sjukhus.

Postoperativ rendezvous ERCP utgör ett alternativ till peroperativ rendezvous ERCP för behandling av sten i djupa gallvägarna, som upptäcks under pågående galloperation, i de fall ERCP-resurser saknas eller är begränsade.

Kirurgi och ERCP utgör likvärdiga behandlingsmetoder för sten i djupa gallvägarna avseende risken för hjärt-kärl komplikationer.

Högre undersökningsvolym av ERCP på skopist- och enhetsnivå är korrelerad till säkrare och mer lyckosam ERCP.

Acknowledgements

I would like to acknowledge and express my sincere gratitude to everyone who has supported me in my work of this thesis. A special thanks to the following persons:

My principal supervisor, Associate Professor **Staffan Eriksson**: For your fantastic support, encouragement, and wise counselling. As far as I know, you have never performed an ERCP in your entire life! Even so I could never have hoped for a more professional guide on my journey.

My co-supervisor, Associate Professor **Gabriel Sandblom**: For excellent help with virtually everything at any time, especially with the statistical analyses. This thesis would not have been written without you.

My co-supervisor Professor **Lars Enochsson**: For sharing your extensive scientific knowledge, and for your wise advice which has been of great value in the research process. Thanks to you I will always bear in mind the former world pole vault champion (stavhopp) Sergej Bubka when planning a new research project.

My co-supervisor **Arne Eklund** PhD: For your excellent support, sharing research ideas and providing insightful comments on the manuscripts. I really appreciate your friendship and our happy moments both inside and outside the ERCP room.

My co-supervisor Professor **Bengt Isaksson**: For your many constructive ideas during the research process and for great support and inspiration.

Co-author, **Johanna Österberg** PhD: For your valuable, knowledgeable, and well-advised contribution to Study IV.

Head of Department of Surgical Sciences, Uppsala University, professor **Per Hellman**, for kind assistance in research questions and contributing to create a great research climate.

Former Heads of Department of Surgery, Uppsala University Hospital, **Kristiina Ahlgren** and **Peter Stålberg**: For giving me the opportunity to combine research studies and clinical work in advanced endoscopy.

Head of Department of Surgery and former Head of Hepato-Pancreatico-Biliary (HPB) Division, Uppsala University Hospital, **Bengt Isaksson**: For your great encouragement, positive energy, and ability to make things happen. Citation from our morning meeting autumn 2019 when Bengt was Head of the HPB-division: "Good morning, this day will be a bit tricky (knepig) to put together, but with some knockout pingpong (rundpingis)" everything will work out fine in the end." Bengt, I am so happy to have been given the opportunity to work with you and the colleagues at HBP!

My fantastic fellow surgeons at the Division of Hepato-Pancreato-Biliary Surgery, **Britt-Marie Karlson Christopher Månsson, Ann Langerth, Farima Brandt, Petter Früling, Laura Zarantonello, Nina Farrokhnia, Jon Unosson, Selma Kabous, Hanna Sternby** and Head of HPB-division, **Jozef Urdzic**: Thanks for the great discussions we have shared at work and all the nice lunches at "Heat" and "Kannan". A special warm thanks to **Britt-Marie** for indispensable theoretical and practical support concerning ERCP and advanced endoscopy, and for being a great colleague and friend.

The excellent ERCP team at Uppsala University Hospital (doctors, nurses, and GallRiks- and ERCP-coordinators), **Olof Persson, Mona Hansson, Sofia Österberg, Maarit Kokkonen, Jessica Lövgren, Annika Raiend Ekfeldt and her colleagues at the operation ward, Gudrun Berglund, Johanna Berlin, Rebecca Dautovic Bergström, Jaqueline Gradin, Mikael Ljungdahl, Peter Moberger, Ann Langerth, Britt-Marie Karlson and Maria Söderström**: For making every-day work a joy and for sharing passion for ERCP.

Gustav Liedberg: Who first opened my eyes to advanced endoscopy when he introduced me to intraoperative ERCP at Kullbergska sjukhuset, Katrineholm 2003, during my time as resident in general surgery.

Urban Arnelo: For invaluable support and teaching during my ERCP fellowship at Karolinska University Hospital, Huddinge.

Fredrik Swahn: For great inspiration, and for allowing me to use your professional drawings of rendezvous ERCP in my book. I certainly share your fascination for endoscopy, and your encouragement has led me to choose "the Right side".

Martin Ljungman: For sharing with me your excellent photos of postoperative rendezvous ERCP and for great mentorship. I really appreciate your stable and calm guidance in the ERCP room in Västerås, especially on those occasions when I got lost in the duodenum or whenever a difficult papilla appeared.

Head of Centre for Clinical Research (CKF), Västerås, **Kent Nilsson and colleagues, especially Maria Pettersson, Mariana Ehn and Maria Dell Uva Karlsson**: for all your professional administrative support and constructive feed-back during this research project.

Centre for Clinical Research (CKF) and the Västmanland Research Fund against Cancer: For financial support.

Lucy Bai: For professional help with the front page illustration.

All my fantastic friends, no one mentioned no one forgotten, for all joy and all nice moments we have spent together.

My wonderful husband **Johan**: For outstanding support throughout this thesis as well as in all aspects of life over the years. You have the unique ability to create a calm and safe atmosphere around you, even in the most stressful situations, and to make other people feel good. I will always love you. **Aron and Joar**, my beloved children: For always reminding me what is most important in life. My mother **Monika**: For great encouragement and for always being there for me. My brother **Per-Olof**: For many exciting moments and laughter together, and for sharing with me the "Syrén spirit". **Marie**, my sister-in-law: For valuable friendship and pleasant company, merci beaucoup. My godchildren **Theo and Tina**: For lots of fun in Kvicksund, Sundbyberg, and Mariefred. **Andrea and Martina**, my children's half-sisters: I am so happy to have had the privilege to get to know you.

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Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography

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Background: **The risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) could be related to technical or patient-related factors. The aim of this study was to assess whether clinical variables and co-morbidities influence the risk of developing PEP.**

Methods: **Data were retrieved from the Swedish GallRiks registry, including all ERCP procedures performed in 2006–2014 for common bile duct stones. A total of 15 800 procedures were identified and cross-checked. Univariable and multivariable logistic regression analyses were conducted with the endpoint of PEP using the following co-variables: age, sex, ASA grade, previous history of acute pancreatitis, diabetes, hyperlipidaemia, hypercalcaemia, kidney disease and liver cirrhosis.**

Results: **Women (odds ratio (OR) 1·33, 95 per cent c.i. 1·14 to 1·55), patients aged less than 65 years (OR 1·68, 1·45 to 1·94), patients with hyperlipidaemia (OR 1·32, 1·02 to 1·70) and those with a previous history of acute pancreatitis (OR 5·44, 4·68 to 6·31) had a significantly increased risk of PEP. In a subgroup analysis of patients with a previous history of acute pancreatitis, the mean time from previous pancreatitis to ERCP was 4423 days in patients who developed PEP *versus* 6990 days in patients who did not ($P = 0·037$). However, when the previous episode of pancreatitis had occurred more than 30 days before ERCP, this association was no longer significant ($P = 0·858$). Patients with diabetes had a decreased risk of PEP (OR 0·64, 0·48 to 0·85).**

Conclusion: **Age, sex, hyperlipidaemia and previous history of recent acute pancreatitis increase the risk of PEP. The reduced risk of PEP in patients with diabetes should be explored in future studies.**

Funding information
The Bengt Ihre Research Fund
The Rickard and Rut Julin Research Fund

Paper accepted 25 February 2019
Published online in Wiley Online Library (www.bjsopen.com). **DOI:** 10.1002/bjs5.50162

Introduction

One of the most feared complications described after endoscopic retrograde cholangiopancreatography (ERCP) is post-ERCP pancreatitis (PEP), which occurs with an incidence of 3·5–5 per cent[1,2]. PEP is defined[3] as 'clinical pancreatitis with amylase at least three times the upper limit of normal at more than 24 h after the procedure requiring hospital admission or prolongation of planned admission', whereas its severity has been based mainly on the length of hospital stay.

The risk of developing PEP can be assessed in relation to several variables, including technical factors (manipulation and injection of contrast into the pancreatic duct, cannulation attempts lasting more than 5 min, and biliary balloon sphincter dilatation) and patient-related factors such as female sex, younger age, sphincter of Oddi dysfunction[2–5] and a previous history of PEP or pancreatitis[6]. The most common causes of acute pancreatitis are biliary stone and alcohol abuse. However, other conditions, including long-term haemodialysis or peritoneal dialysis, are associated with an increased risk[7,8], and co-morbidities such

Table 1 ICD codes for the different conditions

	ICD9	ICD10
Acute pancreatitis		K85
Diabetes (all)	250	E10
		E11
		E12
Diabetes type 1		E10
Liver cirrhosis	456C	I85
	571	K70.3
		K71.7
		K74
Hyperlipidaemia		E78
Hypercalcaemia		E83.5
Kidney disease	402A	I12.0
	402B	I13.1
	403B	N03.2–N03.7
	403X	N05.2–N05.7
	582	N19
	583A–583H	N25.0
	585	Z49.0–Z49.2
	586	Z94.0
	588A	Z99.2
	V42A	
	V45B	
	V56	

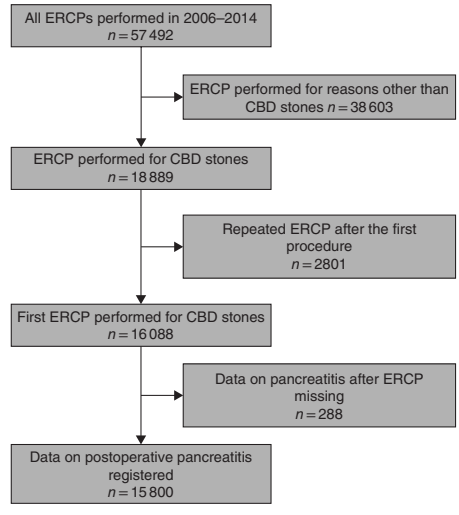

Fig. 1 Flow diagram for the study. ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

as peptic ulcer, hepatic disease and diabetes are frequently described[9].

In particular, patients with type 2 diabetes have a 1·91-fold increased risk of developing biliary disease and a 2·83-fold increased risk of pancreatitis[10]. An increased risk of pancreatitis has also been shown to be associated with younger age and the presence of hypertriglyceridaemia[11], and a reduced risk associated with the use of insulin and long-term use of metformin in diabetic patients[12]. Finally, patients with more advanced cirrhosis (Child–Pugh grade B and C) have a higher incidence of ERCP complications than those with Child–Pugh grade A[13], and an increased risk of postprocedure bleeding, although not of PEP[14].

The aim of the present study was to investigate the risk of PEP in patients with diabetes, liver cirrhosis, hyperlipidaemia, hypercalcaemia and kidney disease.

Methods

Data in the GallRiks registry (the Swedish National Quality Register for Gallstone Surgery and ERCP) were retrieved and reviewed. GallRiks was started in 2005 and includes approximately 90 per cent of cholecystectomies and ERCPs performed in Sweden. GallRiks is regularly externally validated, and the validation process and its national coverage results are published each year[15–17]. Records include patient- and procedure-related data as well as intraoperative and postoperative complications up to 30 days after ERCP.

For the present study, all ERCP procedures registered in GallRiks between 2006 and 2014 for bile duct stones were included. ERCPs conducted for other indications,

Table 2 Baseline characteristics of patients with pancreatitis after endoscopic retrograde cholangiopancreatography registered in the Swedish Nationwide Data Register GallRiks, 2006–2014

	No. of patients (*n* = 15 800)
Age (years)*	64·6(19·1)
Sex	
M	6140 (38·9)
F	9660 (61·1)
ASA fitness grade	
I	5208 (33·0)
II	7484 (47·4)
III	2944 (18·6)
IV	163 (1·0)
V	1 (0·0)
History of acute pancreatitis	2567 (16·2)
Diabetes	1947 (12·3)
Hyperlipidaemia	1394 (8·8)
Hypercalcaemia	58 (0·4)
Kidney disease	579 (3·7)
Liver cirrhosis	185 (1·2)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.).

Table 3 Univariable and multivariable logistic analysis of risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography

	Incidence of post-ERCP pancreatitis*	Univariable analysis		Multivariable analysis‡	
		Odds ratio†	*P*	Odds ratio†	*P*
Age (years)					
≥ 65	349 of 9140 (3·8)				
< 65	416 of 6660 (6·2)	1·68 (1·45, 1·94)	< 0·001		
Sex					
M	250 of 6140 (4·1)				
F	515 of 9660 (5·3)	1·33 (1·14, 1·55)	< 0·001		
History of acute pancreatitis	363 of 2567 (14·1)	5·26 (4·53, 6·10)	< 0·001	5·44 (4·68, 6·31)	< 0·001
Diabetes (all)	56 of 1947 (2·9)	0·55 (0·42, 0·72)	< 0·001	0·64 (0·48, 0·85)	0·002
Diabetes type 1	21 of 564 (3·7)	0·72 (0·47, 1·13)	0·724	0·84 (0·54, 1·31)	0·437
Liver cirrhosis	12 of 185 (6·5)	1·37 (0·76, 2·47)	0·296	1·39 (0·77, 2·51)	0·277
Hyperlipidaemia	72 of 1394 (5·2)	1·08 (0·84, 1·38)	0·556	1·32 (1·02, 1·70)	0·036
Hypercalcaemia	2 of 58 (3·4)	0·70 (0·17, 2·88)	0·622	0·76 (0·18, 3·11)	0·756
Kidney disease	27 of 579 (4·7)	0·96 (0·65, 1·42)	0·838	1·16 (0·78, 1·72)	0·474

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Adjustments were made for sex and age (at least 65 years *versus* less than 65 years). ERCP, endoscopic retrograde cholangiopancreatography.

repeated ERCP (in the same patient) and ERCPs with missing follow-up data were excluded.

PEP was defined as typical abdominal pain, a serum amylase level more than three times the upper limit of normal more than 24 h after ERCP, and the need for hospitalization[3].

Data on chronic disease (diabetes, liver cirrhosis, hyperlipidaemia, hypercalcaemia and kidney disease) and previous episodes of acute pancreatitis were obtained by cross-checking GallRiks data with that in the National Patient Register using ICD codes (*Table 1*).

The Regional Ethics Review Board in Stockholm approved the study (reference number 2015/339-31/1).

Statistical analysis

Univariable and multivariable logistic regression analyses with the endpoint of PEP were performed. In the multivariable analyses, adjustment was made for sex and age (at least 65 years *versus* less than 65 years). Adjustments in the multivariable analysis were made based on assumptions of cause–effect relationships.

A subgroup analysis was conducted in patients with a previous history of pancreatitis. The mean(s.d.) time between the previous episode of pancreatitis and ERCP was determined and compared in patients who developed PEP following ERCP and those who did not have this complication, using Student's *t* test. Statistical analysis was performed with SPSS® version 25 (IBM, Armonk, New York, USA).

Results

Some 15 800 of 57 492 ERCP procedures carried out between 2006 and 2014 that met the study design criteria were analysed (*Fig. 1*). Patient characteristics and risk factors for PEP are shown in *Table 2*.

Table 3 shows the results of univariable and multivariable analyses with the endpoint of PEP. Univariable analysis found a significantly greater risk of PEP in women (odds ratio (OR) 1·33, 95 per cent c.i. 1·14 to 1·55), patients aged less than 65 years (OR 1·68, 1·45 to 1·94) and those with a previous history of acute pancreatitis (OR 5·26, 4·53 to 6·10). Patients with diabetes had a lower risk of PEP (OR 0·55, 0·42 to 0·72). In multivariable analysis, after adjustment for age and sex, a previous history of acute pancreatitis (OR 5·44, 4·68 to 6·31) and hyperlipidaemia (OR 1·32, 1·02 to 1·70) were found to increase the risk of PEP, whereas diabetes decreased the risk (OR 0·64, 0·48 to 0·85).

In a subgroup analysis of 2567 patients with a previous history of acute pancreatitis, the mean(s.d.) time from the previous episode of pancreatitis to ERCP was 4423(5262) days in patients who developed PEP *versus* 6990(5071) days in those who did not develop PEP ($P = 0·037$). However, when the previous episode of pancreatitis had occurred more than 30 days before ERCP, this association was no longer significant. In that group, the mean time from pancreatitis to ERCP was 7772(4747) days in patients who did not develop PEP and 7727(4781) days in those who did ($P = 0·858$).

Discussion

This national register-based analysis found that women, patients aged less than 65 years and those with a previous history of acute pancreatitis had a significantly greater risk of PEP, as documented previously by other authors[2–6]. However, as it is difficult to distinguish a new episode of acute pancreatitis from an exacerbation of an ongoing process, patients with pancreatitis immediately before ERCP were excluded, indicating that an episode of pancreatitis occurring more than 30 days before elective ERCP had no association with the development of PEP.

In accordance with previous studies[11,18] investigating hypertriglyceridaemia, hyperlipidaemia was also found to increase the risk of PEP. However, other associated co-morbidities such as obesity were not investigated in the present study as data on BMI were not available in the registry. Similarly, other possible conditions influencing the risk of PEP, such as alcohol abuse and medications, are not registered consistently in GallRiks.

Although the literature[7,8,19] documents contrasting results with respect to hypercalcaemia/kidney disease and risk of PEP, it should be noted that only 58 patients in the present cohort had hypercalcaemia and 579 had kidney disease, with no data on the degree of renal failure; thus it would be difficult to draw any firm conclusion regarding the association between hypercalcaemia/kidney disease and PEP.

Similar to previous findings[13,14], liver cirrhosis was not found to be a risk factor for PEP.

In contrast to previous studies[10,20], in which diabetes was shown to be associated with acute pancreatitis, a decreased risk of PEP was found in diabetic patients. This was confirmed in the multivariable analysis, after adjustment for age and sex. It has been shown previously[12] that the risk of acute pancreatitis is dependent on the type of diabetes medication received by patients. Although the cohort of diabetic patients consisted of patients on different kinds of diabetic treatment, the registry lacked information on disease severity and treatment; thus these associations were not investigated and need to be validated in future studies.

Disclosure

The authors declare no conflict of interest.

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Paper II

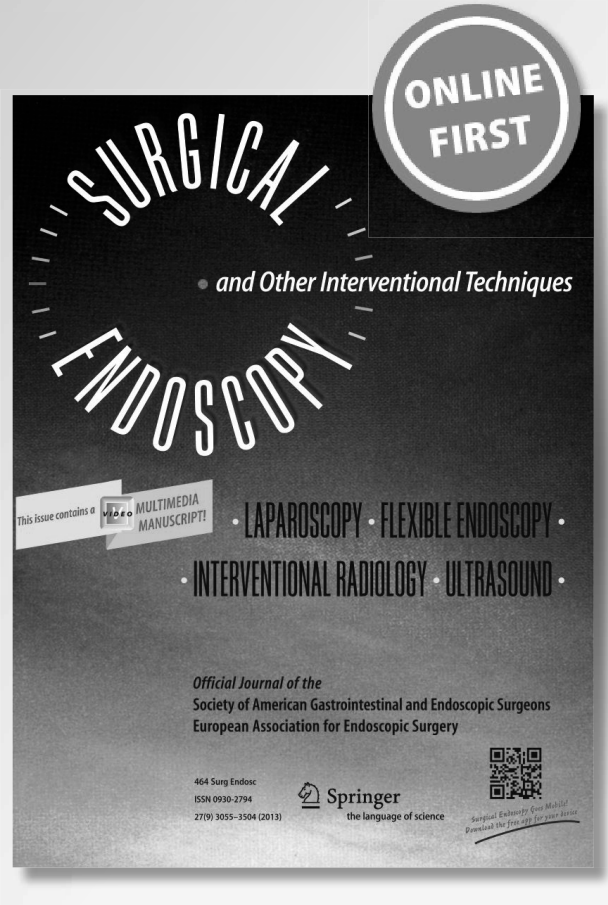
Postoperative rendezvous endoscopic retrograde cholangiopancreaticography as an option in the management of choledocholithiasis

Eva-Lena Syrén, Gabriel Sandblom, Staffan Eriksson, Arne Eklund, Bengt Isaksson & Lars Enochsson

Surgical Endoscopy
And Other Interventional Techniques
Official Journal of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and European Association for Endoscopic Surgery (EAES)

ISSN 0930-2794

Surg Endosc
DOI 10.1007/s00464-019-07272-1



Springer

Surgical Endoscopy
https://doi.org/10.1007/s00464-019-07272-1

Postoperative rendezvous endoscopic retrograde cholangiopancreaticography as an option in the management of choledocholithiasis

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Received: 26 June 2019 / Accepted: 12 November 2019

Abstract

Background Rendezvous endoscopic retrograde cholangiopancreaticography (ERCP) is a well-established method for treatment of choledocholithiasis. The primary aim of this study was to determine how different techniques for management of common bile duct stone (CBDS) clearance in patients undergoing cholecystectomy have changed over time at tertiary referral hospitals (TRH) and county/community hospitals (CH). The secondary aim was to see if postoperative rendezvous ERCP is a safe, effective and feasible alternative to intraoperative rendezvous ERCP in the management of CBDS.

Methods Data were retrieved from the Swedish registry for cholecystectomy and ERCP (GallRiks) 2006–2016. All cholecystectomies, where CBDS were found at intraoperative cholangiography, and with complete 30-day follow-up (n = 10,386) were identified. Data concerning intraoperative and postoperative complications, readmission and reoperation within 30 days were retrieved for patients where intraoperative ERCP (n = 2290) and preparation for postoperative ERCP were performed (n = 2283).

Results Intraoperative ERCP increased (7.5% 2006; 43.1% 2016) whereas preparation for postoperative ERCP decreased (21.2% 2006; 17.2% 2016) during 2006–2016. CBDS management differed between TRHs and CHs. Complications were higher in the postoperative rendezvous ERCP group: Odds Ratio [OR] 1.69 (95% confidence interval [CI] 1.16–2.45) for intraoperative complications and OR 1.50 (CI 1.29–1.75) for postoperative complications. Intraoperative bleeding OR 2.46 (CI 1.17–5.16), postoperative bile leakage OR 1.89 (CI 1.23–2.90) and postoperative infection with abscess OR 1.55 (CI 1.05–2.29) were higher in the postoperative group. Neither post-ERCP pancreatitis, postoperative bleeding, cholangitis, percutaneous drainage, antibiotic treatment, ICU stay, readmission/reoperation within 30 days nor 30-day mortality differed between groups.

Conclusions Techniques for management of CBDS found at cholecystectomy have changed over time and differ between TRH and CH. Rendezvous ERCP is a safe and effective method. Even though intraoperative rendezvous ERCP is the preferred method, postoperative rendezvous ERCP constitutes an acceptable alternative where ERCP resources are lacking or limited.

Keywords Rendezvous ERCP · Choledocholithiasis · Complications

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Laparoscopic cholecystectomy (LC) has become the gold standard worldwide for treatment of gallstone disease. In Sweden about 13.000 cholecystectomies are performed each year and the vast majority of these with minimally invasive surgery [1]. Intraoperative cholangiography (IOC), is routinely performed in Sweden in order to clarify the anatomy of the biliary tree and has also proved to be an effective method to detect common bile duct stones (CBDS) which are found in 10–15% of cases [1–5].

In recent years intraoperative rendezvous endoscopic retrograde cholangiopancreaticography (ERCP) has been established as an alternative method to treat common bile

Published online: 25 November 2019

duct stones discovered during laparoscopic cholecystectomy. This laparo-endoscopic rendezvous (LERV) technique was first described in 1993 by Deslandres et al. [6] and has been shown to have a high rate of CBD stone clearance and a lower complication rate, particularly post-ERCP pancreatitis, compared to conventional ERCP [7–15]. This may be due to the facilitated access to the common bile duct with less manipulation and trauma to the papilla Vateri.

An alternative to the single-session intraoperative ERCP procedure is the postoperative rendezvous ERCP technique, in which the antegrade transcystic guidewire is passed into the duodenum and anchored to the cystic duct with laparoscopic clips. The opposite end of the guidewire is then deviated through the abdominal wall and attached to the skin, leaving the guidewire in situ. The cholecystectomy procedure is completed and the rendezvous ERCP conducted within a few days afterwards using the guidewire to help cannulate the bile duct.

Intraoperative rendezvous ERCP has been recommended as the method of choice rather than postoperative rendezvous ERCP due to lower morbidity, lower costs and shorter hospital stay [16–19]. Nevertheless, the extended operation time and limited access of endoscopic expertise is associated with organizational and logistic challenges with this technique [8, 9, 14]. There are several units in Sweden where cholecystectomies are performed without ERCP resources available. Furthermore, in most of the units where ERCP is an established method for management of common bile duct stones during cholecystectomy, there is no endoscopic expertise available during evenings, week-ends and sometimes not even on a regular basis during weekdays [1].

The primary aim of this nation-wide population-based study was to assess how different techniques for the management of CBDS clearance have changed over time at TRHs and CHs. The secondary aim was to see if postoperative rendezvous ERCP is a safe, effective and feasible alternative to intraoperative rendezvous ERCP in the management of CBDS clearance and complications.

Materials and methods

The study was based on a cohort of prospectively registered data from GallRiks (The Swedish National Quality Registry for Gallstone Surgery and ERCP) 2006–2016.

GallRiks started 1st of May 2005 and covers about 90% of all cholecystectomies and ERCPs in Sweden. All ERCPs are registered-, together with patient- and procedure-related data. All intra- and postoperative complications are registered, and the completeness of 30-day follow-up of postoperative complications, including post-ERCP pancreatitis (PEP), is approximately 95%. PEP is defined according to the Cotton criteria [20]. GallRiks is regularly externally validated [21, 22].

In the case of choledocholithiasis found at cholecystectomy, data were registered in GallRiks as one of the following treatment alternatives: "open choledochotomy"; "transcystic stone extraction"; "flushed or manipulated stones"; "laparoscopic choledochotomy"; "intraoperative ERCP/rendezvous ERCP"; "preparation for postoperative ERCP/rendezvous ERCP"; or "no further procedure".

Data on methods used to treat CBDS during scheduled and acute cholecystectomies at tertiary referral hospitals and county and community hospitals were collected (Figs. 1, 2). In Sweden there are seven university hospitals/tertiary referral hospitals and 65 county and community hospitals.

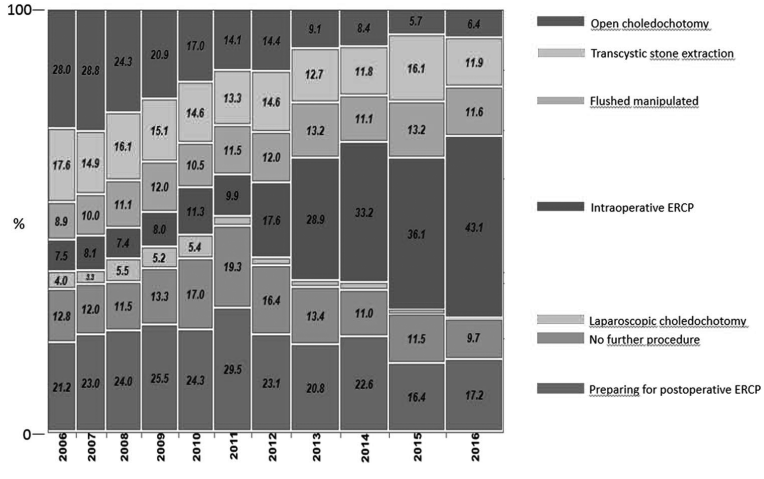

Fig. 1 Alternative techniques for management of CBDS found at cholecystectomy in Sweden 2006–2016

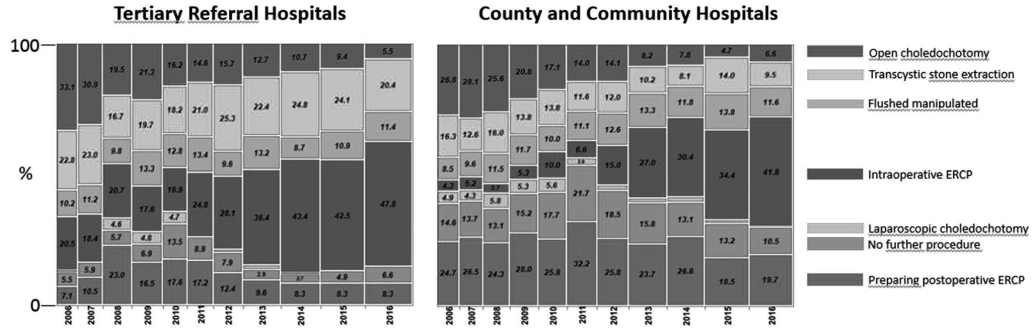

Fig. 2 Frequency of intraoperative ERCP and preparing postoperative ERCP as alternatives to treat CBDS discovered during cholecystectomy at Tertiary Referral Hospitals compared with County and Community Hospitals in Sweden 2006–2016

The primary outcome of this study was changes in techniques used for management of common bile duct stone (CBDS) clearance over time at TRHs and CHs. The secondary outcome was intraoperative and postoperative complications, stone clearance and mortality with postoperative rendezvous ERCP compared to intraoperative rendezvous ERCP. The intraoperative complications analyzed were overall complications and bleeding and the postoperative complications included overall complications, bleeding, pancreatitis, cholangitis, bile leakage, infection with abscess, percutaneous drainage, antibiotic treatment, ICU stay, readmission and reoperation within 30 days (as a proxy for stone clearance rate/retained stones) and 30-day mortality. We have also analyzed length of hospital stay.

The Regional Ethics Review Board in Uppsala approved the study the 18th of September 2018 (Reference Number: 2016/281/1) after a complementary application to the original ethics approval from 2nd of November 2016 (Reference Number: 2016/281/1).

Statistics

Univariate and multivariate regression analyzes were used as well as Pearson Chi Square Test and Student's *T* Test.

The analyzes were based on patients undergoing cholecystectomy with intraoperative ERCP and patients undergoing cholecystectomy as well as postoperative ERCP in two separate procedures. The complication rate was determined by extracting intraoperative and postoperative complications within 30 days after the cholecystectomy as well as the postoperative ERCP. In univariate and multivariate logistic regression analysis, the odds ratio for intra- and postoperative complications was determined, adjusted for gender, age and ASA score.

Statistical significance was defined as $p < 0.05$. Statistical analysis was carried out using JMP® Pro version 14.0.0 (SAS Institute Inc., USA).

Results

In this study all cholecystectomies performed 2006–2016, where CBDS were found at intraoperative cholangiography and 30-day follow-up was complete were included. In total 10,386 procedures fulfilled the criteria (Fig. 3). Data for CBDS clearance and complications were retrieved for intraoperative rendezvous ERCP (n = 2290) as well as for

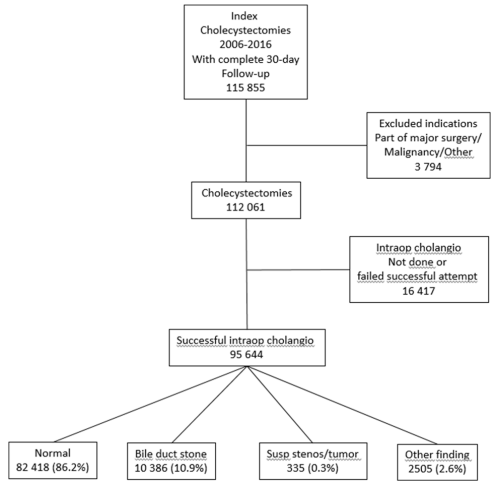

Fig. 3 Flowchart cholecystectomies in Sweden 2006–2016

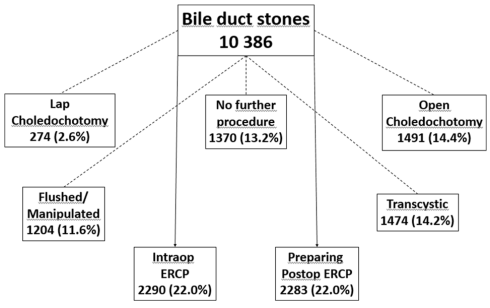

Fig. 4 Flowchart common bile duct stones in Sweden 2006–2016

Table 1 Demographics of the two groups: intraoperative and preparing postoperative ERCP, ERCP within 30 days

	ERCP		*P*
	Intraop n = 2290	Preparing postop n = 2283	
Females[a]			
n	**1493**	**1536**	
%	65.2	67.3	
Males			
n	**797**	**747**	
%	34.8	32.7	
Total			
n	**2290**	**2283**	0.1363
ASA 1-2			
n	**2071**	**2104**	
%	90.4	92.2	
ASA > 2			
n	**219**	**179**	
%	9.6	7.8	**0.0388**
Age[b] (years)			
Mean	**51.3**	**52.9**	
SEM	0.4	0.4	**0.0023**

Statistically significant values are given in bold

[a]Pearson ChiSquare

[b]Student's *t* test

procedures where preparation for postoperative rendezvous ERCP was undertaken (n = 2283, Fig. 4).

Patients in the group with preparation for postoperative rendezvous ERCP were slightly older. More patients in the intraoperative ERCP group had an ASA score > 2. There were no gender-specific differences between the two groups (Table 1).

The percentage intraoperative ERCP procedures increased from 7.5 to 43.1% during the study period, and since 2013 it has been the predominant method for management of CBDS found at cholecystectomy. Preparation for postoperative rendezvous ERCP, on the other hand, gradually decreased during the final years of the study period, 21.2% in 2006 and 17.2% in 2016 (Fig. 1).

Management of CBDS differ between TRHs and CHs. The most commonly used method was intraoperative ERCP, though this option was more commonly used at TRHs; 47.8% (2016) compared to 41.8% at CHs. On the other hand, preparation for postoperative rendezvous ERCP was more frequent in CHs; 19.7% (2016) compared to 8.3% at TRHs (Fig. 2).

The intraoperative complication rate was lower in the intraoperative rendezvous ERCP group compared to the postoperative rendezvous ERCP group (2.0% vs. 3.4%; p = 0.0031). The same pattern was noted regarding postoperative complication rates (15.6% vs. 21.8%; p < 0.0001).

Intraoperative bleeding rate was lower in the intraoperative rendezvous ERCP group compared to the postoperative ERCP rendezvous group (0.4% vs. 1.1%; p = 0.0106).

There were no significant differences between the two groups regarding postoperative bleeding, pancreatitis, cholangitis, percutaneous drainage, antibiotic treatment, ICU stay or reoperation within 30 days.

Postoperative bile leakage and infection with abscess rates were lower in the intraoperative ERCP group compared to the postoperative rendezvous ERCP group (1.4% vs. 2.7%; p = 0.0025 and 1.9% vs. 2.9%; p = 0.0197 respectively).

Readmission rate within 30 days and 30-day mortality were higher in the intraoperative ERCP group (0.7% vs. 0.3%; p = 0.0498 and 0.31% vs. 0.04%; p = 0.0341 respectively) (Table 2).

In the multivariate analzses overall intraoperative and overall postoperative complications, intraoperative bleeding, postoperative bile leakage and postoperative infection with abscess were all significantly higher in the postoperative rendezvous ERCP group. The Odds Ratio for overall complications in the postoperative rendezvous ERCP group with the intraoperative ERCP group as a reference was 1.69 (CI 1.16–2.45) intraoperatively, and 1.50 (CI 1.29–1.75) postoperatively. The odds ratio for intraoperative bleeding was 2.46 (CI 1.17–5.16), for postoperative bile leakage 1.89 (CI 1.23–2.90) and for postoperative infection with abscess 1.55 (CI 1.05–2.29) (Table 3).

The total length of hospital stay was somewhat shorter for patients who underwent intraoperative ERCP compared to patients who were prepared for postoperative ERCP (Table 4).

Discussion

In this study, based on prospectively assembled population-based data from GallRiks, we compared methods of managing CBDS found at intraoperative cholangiography in a

Table 2 Intra- and postoperative complications n (%), ERCP within 30 days

	Intraop ERCP n (%)	Preparing postop n (%)	P^a
Intraoperative complications			
Overall	45 (2.0)	77 (3.4)	**0.0031**
Bleeding	10 (0.4)	25 (1.1)	**0.0106**
Postoperative complications			
Overall	357 (15.6)	497 (21.8)	**<0.0001**
Bleeding	28 (1.2)	20 (0.9)	0.2501
Pancreatitis	108 (4.7)	101 (4.4)	0.6362
Cholangitis	14 (0.6)	21 (0.9)	0.2314
Bile leakage	33 (1.4)	62 (2.7)	**0.0025**
Infection with abscess	43 (1.9)	67 (2.9)	**0.0197**
Percutaneous drainage	51 (2.2)	69 (3.0)	0.0925
Antibiotic treatment	223 (9.7)	237 (10.4)	0.4697
ICU stay	6 (0.3)	3 (0.1)	0.3191
Readmission within 30 days	15 (0.7)	6 (0.3)	**0.0498**
Reop within 30 days	46 (2.0)	48 (2.1)	0.8232
Mortality 30 days	7 (0.31)	1 (0.04)	**0.0341**

Statistically significant values are given in bold

[a]Pearson ChiSquare

Table 3 Intra- and postoperative complications of preparing for postoperative versus intraoperative ERCP (reference)

	Intraop ERCP ref		
	OR	95% CI	*P*
Intraoperative complications			
Overall	1.69	(1.16–2.45)	**0.0061**
Bleeding	2.46	(1.17–5.16)	**0.0170**
Postoperative complications			
Overall	1.50	(1.29–1.75)	**< 0.0001**
Bleeding	0.72	(0.40–1.28)	0.2581
Pancreatitis	0.95	(0.72–1.25)	0.7053
Cholangitis	1.53	(0.77–3.02)	0.2229
Bile leakage	1.89	(1.23–2.90)	**0.0034**
Infection with abscess	1.55	(1.05–2.29)	**0.0270**
Percutaneous drainage	1.34	(0.93–1.94)	0.1191
Antibiotic treatment	1.06	(0.88–1.29)	0.5336
ICU stay	0.51	(0.13–2.04)	0.3394
Readmission within 30 days	0.41	(0.16–1.07)	0.0681
Reop within 30 days	1.05	(0.70–1.58)	0.8146
Mortality 30 days	0.16	(0.02–1.35)	0.0927

ERCP within 30 days. Multivariate analysis

Adjusted for gender, age and ASA

Statistically significant values are given in bold

Table 4 Length of stay (days)

Intraop ERCP		Preparing postop ERCP		
Mean	SEM	Mean	SEM	*p*
4.7	0.1	5.1	0.1	0.0454

large number of cholecystectomies over a long period of time. We surveyed the management of CBDS over time as well as differences between tertiary referral hospitals compared to community/county hospitals. The decision on treatment regimens is mainly based on local traditions at each respective hospital. There are units where cholecystectomies are performed on regular basis but where there is a lack of ERCP resources. At such units, two-stage procedures are the only choice besides transcystic stone extraction or extraction by choledochotomy.

We focused on the two most common treatment options regarding choledocholithiasis; intraoperative and postoperative rendezvous ERCP and compared these methods regarding intraoperative and postoperative complication rates as well as readmission, reoperation and mortality. In recent years intraoperative rendezvous ERCP has been established as the method of choice in many units where ERCP resources at cholecystectomy are available. The result of this is that it has not been possible to conduct a prospective randomized-controlled trial comparing the two methods.

CBDS are commonly found during cholecystectomy when intraoperative cholangiography (IOC) is routinely performed [15]. Open choledochotomy, traditionally considered the first-hand technique for managing CBDS, has decreased in recent years. On the other hand, minimally invasive laparoscopic and laparo-endoscopic methods have become more frequently used. There are several strategies to manage CBDS but the optimal method as well as timing is still under debate [5, 16, 23–30].

ERCP is a well-established method for treatment of diseases of the common bile ducts, including bile duct calculi [1, 31]. ERCP has traditionally been performed as a two-stage procedure, either as preoperative ERCP followed by laparoscopic cholecystectomy or laparoscopic cholecystectomy followed by postoperative ERCP. However, 4–18% of attempted ERCPs fail due to inability to cannulate the bile duct [1, 32]. ERCP may also lead to serious complications, of which post-ERCP pancreatitis (PEP) is the most frequent with an incidence of 3.5–5% [1, 33]. The risk of developing PEP depends on patient-related factors such as female gender, younger age and Sphincter of Oddi dysfunction [34]. Technical factors such as manipulation of and injection of contrast into the pancreatic duct, biliary balloon sphincter dilation and cannulation attempts lasting > 5 min, also increase the risk [33, 35, 36].

Intraoperative rendezvous ERCP is an effective and safe method to treat CBDS found at cholecystectomy and concomitant cholangiography [7–14]. The operative technique of laparo-endoscopic rendezvous is straight-forward and suitable for almost all patients with CBDS. In this way cholecystectomy and management of CBDS are performed in a single procedure, thereby limiting anesthesia to one occasion and minimal hospital stay, health care resources and costs. In Sweden, therefore, at hospitals where ERCP is available, intraoperative rendezvous ERCP has been the method of choice in the management of CBDS during cholecystectomy.

In this study we have shown that during the period 2006–2016, intraoperative ERCP gradually became the predominating method to manage CBDS at all hospital levels in Sweden and by 2016 60% of patients were managed this way. Intraoperative rendezvous ERCP was the method of choice at all hospital levels, but most commonly used in TRHs. Preparing for postoperative rendezvous ERCP, on the other hand, was performed twice as often in CHs compared to TRHs. In 2016 postoperative rendezvous ERCP was the second most common method of managing CBDS in these hospitals compared to only the fourth most common method at TRHs, probably due to a lack of resources for performing intraoperative ERCP in non-specialized centers.

The complication rate regarding intraoperative ERCP and preparing postoperative ERCP is assessed intraoperatively (overall complications, bleeding) as well as 30 days after the procedure (overall complications, bleeding, pancreatitis, cholangitis, bile leakage, infection with abscess, percutaneous drainage, antibiotic treatment, ICU stay, readmission, reoperation, mortality). Since intraoperative ERCP is conducted simultaneously with the cholecystectomy and postoperative ERCP in most cases is performed within 1 or 2 days after cholecystectomy we cannot exclude that some of the observed complications could have been caused by the cholecystectomy rather than the ERCP.

The overall incidence of intra- and postoperative complications as well as intraoperative bleeding, postoperative bile leakage and postoperative infection with abscess was higher in postoperative rendezvous ERCP compared to intraoperative rendezvous ERCP. Manipulation of the guidewire preparing for postoperative ERCP could be one possible explanation for a higher rate of postoperative bile leakage and infection in this group. If the clips around the cystic duct, anchoring the guide wire, are applied too loose there probably is a risk for subsequent bile leakage.

The rate of the most common surgical complication, post-ERCP pancreatitis, was not significantly higher in patients treated with postoperative rendezvous ERCP, neither were postoperative bleeding, cholangitis, need for percutaneous drainage, antibiotic treatment, ICU stay or 30-day mortality.

Readmission and reoperation within 30 days rates, a proxy for stone clearance and effectiveness of the ERCP procedure, were also similar between the groups.

Since many cholecystectomies are performed in hospitals where ERCP is not performed at all, or performed during off-hours when access to ERCP is limited, there is a need for an alternative management solution. Preparing for postoperative rendezvous ERCP by leaving a guidewire for later definitive treatment of CBDS the days following cholecystectomy is a feasible alternative. The routine of leaving a guidewire through the abdominal wall bandaged to the skin cause some discomfort to the patient, even if most patients seem to tolerate the guidewire quite well.

Based on the results of this study we believe that laparo-endoscopic biliary duct stone clearance techniques are safe and effective. Intraoperative rendezvous ERCP is the method of choice due to a lower complication rate and optimal utilization of hospital resources. Postoperative rendezvous ERCP constitutes an acceptable alternative in situations where ERCP resources are lacking or limited. It is technically easier to perform compared to non-rendezvous postoperative ERCP since the cannulation of the common bile duct is facilitated by a guide wire to the duodenum. This often renders the ERCP procedure faster, with less risk of traumatizing the papilla with subsequent oedema and in some cases PEP.

Acknowledgments Open access funding provided by Uppsala University.

Compliance with ethical standards

Disclosures Drs. Syrén, Sandblom, Eriksson, Eklund, Isaksson and Enochsson have no conflicts of interest or financial ties to disclose.

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Paper III

Surgical Endoscopy
https://doi.org/10.1007/s00464-020-07766-3

Cardiovascular complications after common bile duct stone extractions

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Received: 31 March 2020 / Accepted: 25 June 2020

Abstract

Background Common bile duct stone (CBDS) is a common condition the rate of which increases with age. Decision to treat in particular elderly and frail patients with CBDS is often complex and requires careful assessment of the risk for treatment-related cardiovascular complications. The aim of this study was to compare the rate of postoperative cardiovascular events in CBDS patients treated with the following: ERCP only; cholecystectomy only; cholecystectomy followed by delayed ERCP; cholecystectomy together with ERCP; or ERCP followed by delayed cholecystectomy.

Methods The study was based on data from procedures for gallstone disease registered in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography (GallRiks) 2006–2014. ERCP and cholecystectomy procedures performed for confirmed or suspected CBDS were included. Postoperative events were registered by cross-matching GallRiks with the National Patient Register (NPR). A postoperative cardiovascular event was defined as an ICD-code in the discharge notes indicating myocardial infarct, pulmonary embolism or cerebrovascular disease within 30 days after surgery. In cases where a patient had undergone ERCP and cholecystectomy on separate occasions, the 30-day interval was timed from the first intervention.

Results A total of 23,591 underwent ERCP or cholecystectomy for CBDS during the study period. A postoperative cardiovascular event was registered in 164 patients and death within 30 days in 225 patients. In univariable analysis, adverse cardiovascular event and death within 30 days were more frequent in patients who underwent primary ERCP ($p < 0.05$). In multivariable analysis, adjusting for history of cardiovascular disease or events, neither risk for cardiovascular complication nor death within 30 days remained statistically significant in the ERCP group.

Conclusions Primary ERCP as well as cholecystectomy may be performed for CBDS with acceptable safety. More studies are required to provide reliable guidelines for the management of CBDS.

Keywords ERCP · Choledocholithiasis · Cardiovascular complication

Common bile duct stone (CBDS) is a common disease with varying clinical manifestations. CBD stones are often asymptomatic, but may cause biliary pancreatitis, obstructive jaundice, cholangitis, or recurrent pain [1, 2]. There are several accepted methods of treatment for CBDS [3–8]. Cholecystectomy with or without concomitant intraoperative rendezvous endoscopic retrograde cholangiopancreaticography (ERCP), if CBDS is found on intraoperative cholangiography (IOC), is a well-established, safe and cost-effective method for patients considered fit for surgery [9–12].

ERCP is sometimes performed as part of a two-stage procedure, either as ERCP followed by delayed cholecystectomy or cholecystectomy followed by delayed ERCP [1, 13]. In some patients, where high age and comorbidity render them too high risk for surgery, ERCP with sphincterotomy and stone extraction may be preferred as sole intervention, even if recurrent choledocholithiasis is more common

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Published online: 01 July 2020

when ERCP is the only treatment performed [14]. If ERCP is performed without the aid of antegrade introduction of a guidewire at IOC, 4–18% of attempts fail due to inability to cannulate the bile duct [9]. Surgical complications, especially post-ERCP pancreatitis (PEP), are also more frequent after standard ERCP compared to rendezvous ERCP [10, 11, 15–17].

The frequency of CBDS increases with age. This complicates management as comorbidity and frailty increase the risk for intervention-related complications. Cardiovascular disease and biliary stone disease share risk factors such as obesity, hypertension, diabetes, dyslipidemia, and cigarette smoking [18–20]. There also appears to be an association between gallstone disease and cardiovascular disease [21].

The cardiovascular complication and pulmonary thromboembolism (PTE) rates following laparoscopic cholecystectomy and ERCP are low, even in elderly patients (< 2%) [22–25].

The aim of this study was to compare postoperative cardiovascular complication rates (myocardial infarct, pulmonary thromboembolism and/or cerebrovascular disease) in patients with CBDS treated with: ERCP only; cholecystectomy only; cholecystectomy followed by delayed ERCP; cholecystectomy combined with ERCP; or ERCP followed by delayed cholecystectomy.

Materials and methods

This study was based on procedures for gallstone disease registered in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography (GallRiks) 2006–2014. GallRiks registration began 1st May 2005 and now covers approximately 90% of all cholecystectomies and ERCPs performed in Sweden, including patient- and procedure-related data. All intra- and postoperative adverse events, including cardiovascular complications, are registered, and the completeness of 30-day follow-up of postoperative complications is approximately 95%. GallRiks is regularly externally validated [26, 27].

In the present study, ERCP as well as cholecystectomy performed with confirmed or suspected CBDS as indication were included. Patients who underwent cholecystectomy combined with ERCP were also included as long as either of the procedures was performed with CBDS as indication. ERCP or cholecystectomy performed because of malignant stricture or suspicion of cancer were excluded as well as patients who underwent one or more procedures without CBDS as indication.

Patients with confirmed or suspected CBDS were divided into five treatment groups: ERCP only; cholecystectomy only; cholecystectomy followed by delayed ERCP, cholecystectomy combined with ERCP; or ERCP followed by delayed cholecystectomy.

Postoperative events were registered by cross-matching GallRiks with the National Patient Register (NPR). Data on cardiovascular complications within 30 days after surgery, defined as a diagnosis in the discharge notes with an ICD-code indicating myocardial infarct, pulmonary embolism or cerebrovascular disease (not including those who had an ICD-code indicating cerebrovascular disease prior to surgery), were retrieved from the NPR. If a patient had undergone both ERCP and cholecystectomy, the 30-day interval was timed from the first intervention. Data on previous cardiovascular events were also obtained from the NPR.

The Regional Ethics Review Board in Stockholm approved the study 18th March 2015 (IRB-approval, reference number: 2015/339-31/1).

Consent from the patient to participate in register-based research is required for registration in GallRiks. Patients are given the opportunity to withdraw all their personal data at any time from the register.

Statistics

In order to adjust for confounders, multivariate logistic regression analyses were performed, with cardiovascular event (myocardial infarct and/or pulmonary embolus and/or cerebrovascular disease) and death within 30 days as endpoints. The multivariate models were based on age (≥ 80 years vs < 80 years), ASA score (III–V vs I–II), gender, treatment and history of cardiovascular condition or event (myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular event, diabetes with secondary complication or pulmonary embolism). Patients who underwent cholecystectomy and ERCP during the same procedure and those who underwent cholecystectomy and delayed ERCP were grouped together with the cholecystectomy group, whereas those who underwent ERCP and delayed cholecystectomy were grouped together with the ERCP group. This grouping was based on which procedure was the primary intervention aimed at managing the CBDS.

Poisson regression was used to calculate the 30-day age- and gender-adjusted standardized mortality ratio (SMR) based on the expected mortality rate extrapolated from the Swedish general population in 2007.

Results

During the study period, 103,208 patients underwent cholecystectomy and/or ERCP due to gallstone disease. After excluding cholecystectomies performed without preoperatively diagnosed common bile duct stone and

patients registered with more than one cholecystectomy, 23,591 patients remained in the study group. Of those, 8790 underwent ERCP only, 10,362 cholecystectomy only, 1032 cholecystectomy followed by delayed ERCP, 1258 cholecystectomy combined with ERCP, and 2149 ERCP followed by delayed cholecystectomy (Fig. 1).

Patients in the ERCP only group were older, more often female and ASA grade III–V vs I–I compared to the cholecystectomy only group. A previous history of cardiovascular disease (myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular event, diabetes with secondary complication or pulmonary embolism) was also much more common in the ERCP only group. In the group ERCP

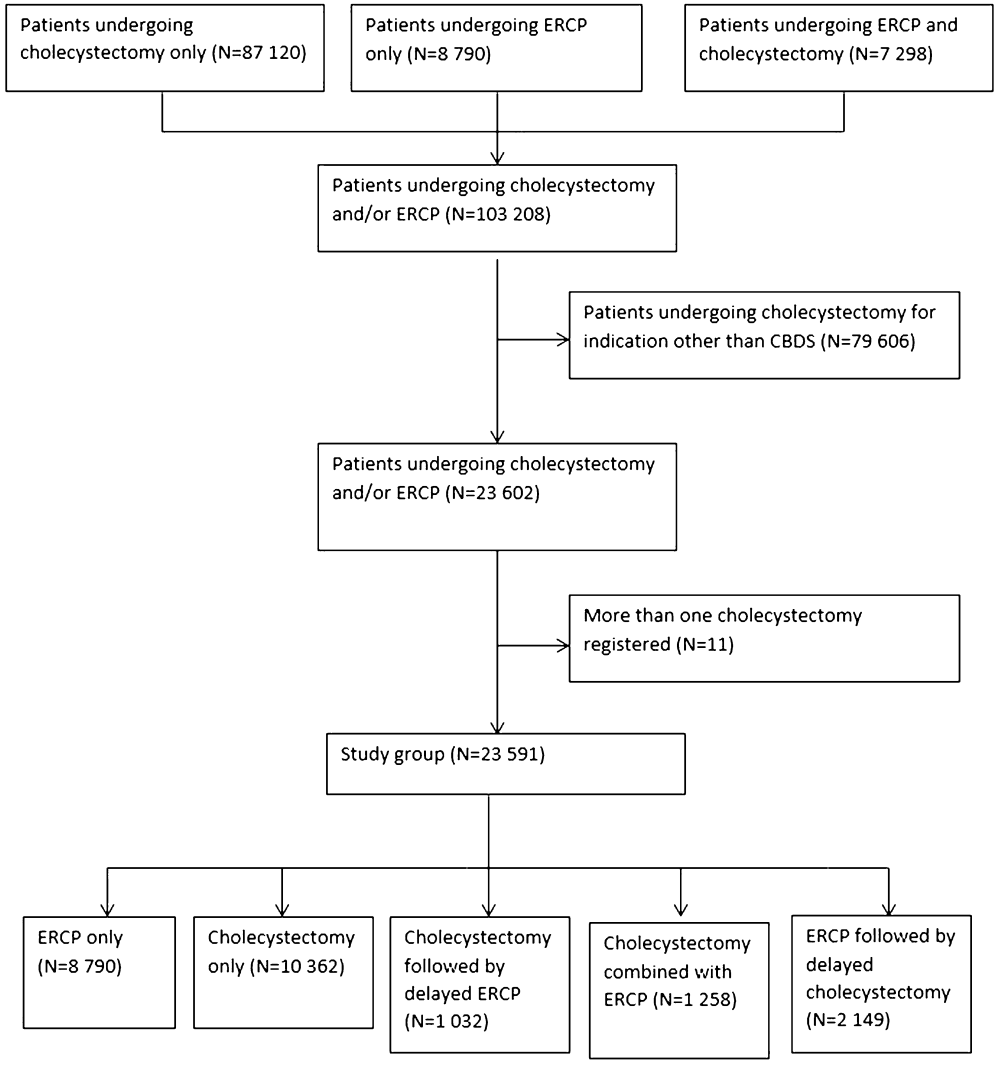

Fig. 1 Flow chart. Confirmed or suspected CBDS as indication for treatment

followed by delayed cholecystectomy, patients were older and more often had a previous history of cardiovascular disease compared to patients in the groups cholecystectomy combined with ERCP, and cholecystectomy followed by delayed ERCP (Table 1).

In all, a postoperative cardiovascular event was registered in 164 cases and death within 30 days in 225 cases. Postoperative adverse event and death within 30 days were more frequently seen in the ERCP only group compared to the other groups. Myocardial infarct was at least twice as common (0.71%) and cerebrovascular lesion at least three times as common (0.26%) in the ERCP only group compared to the other groups. The incidence of pulmonary embolism was more equally distributed between groups and most common in the group cholecystectomy followed by delayed ERCP (0.39%). Postoperative death within 30 days was between 5 and 20 times more common in the ERCP only group (1.97%) (Table 2).

Age ≥ 80 years, ASA > 1 and history of cardiovascular disease or event were all risk factors for postoperative complication and death. In the univariable and multivariable logistic regression analyses, cardiovascular complication and death within 30 days were studied in the ERCP group (ERCP only + ERCP with delayed cholecystectomy), with

Table 1 Baseline characteristics

	ERCP only ($N=8790$)	Cholecystectomy only ($N=10,362$)	Cholecystectomy followed by delayed ERCP ($N=1\,032$)	Cholecystectomy combined with ERCP ($N=1258$)	ERCP followed by delayed cholecystectomy ($N=2149$)
Gender					
Men	3653 (36.1%)	4650 (46.0%)	413 (4.1%)	479 (4.7%)	918 (9.1%)
Women	5137 (38.1%)	5712 (42.4%)	619 (4.6%)	779 (5.8%)	1231 (9.1%)
Mean age, years (standard deviation)	73.5 (15.5)	53.5 (17.8)	55.0 (17.9)	49.4 (18.4)	58.8 (16.1)
ASA					
I	1583 (18.9%)	4631 (56.1%)	429 (5.2%)	646 (7.8%)	980 (11.9%)
II	4627 (41.5%)	4570 (41.0%)	468 (4.2%)	515 (4.6%)	985 (8.7%)
III	2451 (61.9%)	1092 (27.8%)	128 (3.2%)	95 (2.4%)	191 (4.8%)
IV	148 (62.7%)	66 (28.0%)	7 (3.0%)	2 (0.8%)	13 (5.5%)
V	1 (25.0%)	3 (75.0%)	0	0	0
History of cardiovascular disease and events					
Myocardial infarct	1140 (13.0%)	373 (3.6%)	49 (4.7%)	35 (2.8%)	103 (4.8%)
Cardiac failure	1406 (16.0%)	363 (3.5%)	43 (4.2%)	34 (2.7%)	100 (4.7%)
Peripheral vascular disease	691 (7.9%)	209 (2.0%)	19 (1.8%)	26 (2.1%)	72 (3.4%)
Cerebrovascular event	1536 (17.5%)	512 (4.9%)	54 (5.2%)	54 (4.3%)	130 (6.0%)
Diabetes with secondary complication	454 (5.2%)	188 (1.8%)	21 (2.0%)	14 (1.1%)	53 (2.5%)
Pulmonary embolism	270 (3.1%)	112 (1.1%)	16 (1.6%)	7 (0.6%)	26 (1.2%)

Table 2 Postoperative adverse events in confirmed or suspected CBDS within 30 days in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography (GallRiks) 2006–2014

	ERCP only ($N=8790$)	Cholecystectomy only ($N=10,362$)	Cholecystectomy followed by delayed ERCP ($N=1032$)	Cholecystectomy combined with ERCP ($N=1258$)	ERCP followed by delayed cholecystectomy ($N=2149$)	Total complication incidence ($N=164$) and death ($N=225$)
Myocardial infarct	62 (0.71%)	13 (0.13%)	3 (0.29%)	1 (0.08%)	3 (0.14%)	82
Cerebrovascular lesion	23 (0.26%)	5 (0.05%)	1 (0.10%)	0 (0%)	2 (0.09%)	31
Pulmonary embolism	23 (0.26%)	19 (0.18%)	4 (0.39%)	3 (0.24%)	2 (0.09%)	51
Postoperative death	173 (1.97%)	43 (0.41%)	4 (0.39%)	3 (0.24%)	2 (0.09%)	225

the cholecystectomy group as reference (cholecystectomy with or without combined ERCP + cholecystectomy with delayed ERCP). In the univariable analysis, adverse cardiovascular event (OR 2.74, 95% confidence interval [CI] 1.95–3.84, $p < 0.001$) and death (OR 4.10, CI 3.00–5.62, $p < 0.001$) were more frequent in the ERCP group. In the multivariable analysis, adjusting for history of cardiovascular conditions or events, neither the risk for cardiovascular complication (OR 1.12, CI 0.77–1.64, $p < 0.548$) nor death within 30 days (OR 1.38, CI 0.97–1.96, $p < 0.071$) remained statistically significant in the ERCP group (Table 3).

Discussion

In this register-based study, we analyzed postoperative cardiovascular complications in a large number of patients who underwent surgical treatment for confirmed or suspected CBDS. The study was based on prospectively assembled population-based data from GallRiks covering a long period of time. The study focused on the most common postoperative cardiovascular events *i.e.* myocardial infarct and/or pulmonary embolus and/or cerebrovascular disease as well as death within 30 days. Although the study could not show any approach to be safer than the others, our results may help in future treatment-decisions.

We decided to focus on and present only the incidence of cardiovascular complications. There are differences in the burden of cardiovascular disease between Sweden and other parts of the world. U.S. and Swedish data diverge to a lesser extent than what may be seen when the Western World is compared to areas outside Western Europe and North America [28].

The prevalence of gallstone-related symptoms, including CBDS, in the population is high (7–15%) and high age is a significant risk factor for prolonged hospital stay and death after any procedure for gallstone removal [29, 30]. The comorbidity rate in elderly patients undergoing treatment for choledocholithiasis is high compared to younger patients [31]. Frailty is a crucial risk factor, although it is difficult to quantify. We consider age as surrogate measure for frailty, although age and frailty only partly correlate.

Tobacco use and obesity are major risk factors that have to be taken into account when estimating the risk for cardiovascular complications following a surgical or endoscopic intervention. Even if smoking and BMI are included in the ASA physical status they were not registered routinely in GallRiks during the period of the study [32]. We also lack data on medications, including anticoagulation. There was no consistent predetermined national algorithm administration during the period of study. In Sweden the prevailing routine is to interrupt anticoagulation therapy before surgery and ERCP and restart anticoagulation postoperatively, but each hospital follow their own local guidelines.

Anesthesia was not included as predictor in the present study. It has though been explored in a recent study based on GallRiks data which has shown more post-procedural complications occurred after ERCPs performed under deep

Table 3 Univariable and multivariable analyses of factors predicting cardiovascular event and death within 30 days after surgical and/or endoscopic treatment for confirmed or suspected CBDS in the Swedish National Quality Register for Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography (GallRiks) 2006–2014

Univariable	Cardiovascular complication		Death	
	Odds ratio (95% confidence interval)	*p*	Odds ratio (95% confidence interval)	*p*
Age ≥ 80 years (ref < 80 years)	4.37 (3.20–5.60)	< 0.001	9.60 (7.20–12.79)	< 0.001
Men (ref women)	1.16 (0.85–1.59)	0.340	1.19 (0.91–1.55)	0.197
ASA I (ref)				
ASA II	3.83 (2.16–6.79)	< 0.001	6.42 (3.08–13.35)	< 0.001
ASA III	9.82 (5.51–17.52)	< 0.001	31.39 (15.32–64.31)	< 0.001
ASA IV	26.03 (11.44–59.22)	< 0.001	150.02 (67.94–331.23)	< 0.001
ASA V	–	–	343.38 (32.20–3662.14)	< 0.001
History of cardiovascular disease or event[a]	10.20 (7.12–14.60)	< 0.001	6.25 (4.74–8.23)	< 0.001
ERCP (ref cholecystectomy)[b]	2.74 (1.95–3.84)	< 0.001	4.10 (3.00–5.62)	< 0.001
Multivariable	Cardiovascular complication		Death	
ERCP (ref cholecystectomy)[a]	1.12 (0.77–1.64)	0.548	1.38 (0.97–1.96)	0.071

[a]History of myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular event, diabetes with secondary complication or pulmonary embolism

[b]In cases where ERCP as well as cholecystectomy were performed, allocation was determined by the primary procedure. If cholecystectomy and ERCP were performed as one procedure, the procedure was allocated to the cholecystectomy group

sedation compared to those performed under general anesthesia [33].

The five treatment groups in this study are not predetermined and the affiliation to a certain group is dependent on several heterogeneous factors such as complexity and status of the biliary disease and preference of the deciding doctor or local treatment regimes. Several strategies are employed to manage CBDS disease, and methods and timing vary from hospital to hospital [3]. Even if cholecystectomy combined with rendezvous ERCP is standard in many departments, the decision on which treatment is used for CBDS is usually based on local tradition and ERCP-competence. Before the introduction of intraoperative rendezvous ERCP, it was common that patients with CBDS were treated with a two-stage procedure, either preoperative ERCP followed by cholecystectomy or cholecystectomy followed by postoperative ERCP [34]. There are still units where cholecystectomy is performed on regular basis but where there is a lack of ERCP resources and a two-stage procedure thus remains the only choice [34].

Even if early cholecystectomy appears to be safe in elderly, there is a tendency to choose minimally invasive treatment methods such as ERCP when it comes to older, frail patients with comorbidity [35]. No subsequent cholecystectomy was registered for any of the 8790 patients with ERCP as sole intervention. It is, however, possible that some of the patients underwent cholecystectomy after the period of the study. As a cholecystectomy at that late state could not be expected to be performed with the aim of preventing CBDS, we do not think that they are relevant for the aims of the present study.

It is possible that procedure-related complications preceded the cardiovascular complications, which also has to be taken into account when deciding on treatment of common bile duct stones. Even if we believe that most complications are included, it can't be excluded that registration of some adverse events could have been missed in the analysis regarding those patients who underwent both ERCP and cholecystectomy as two separate interventions and with a long interval between procedures.

In this study patients who were selected for ERCP were older and had more comorbidity than patients in the other treatment groups. Myocardial infarction, cardiac failure, peripheral vascular disease, cerebrovascular event, diabetes with secondary complication and pulmonary embolism were strong predictors for cardiovascular complication and death after surgical treatment for CBDS. We believe that the selection of frail patients and patients with greater comorbidity for ERCP explains why ERCP was significant in univariate analysis. In multivariable analysis, adjusting for history of cardiovascular disease or events, neither risk for cardiovascular complication nor death within 30 days remained statistically significant in the ERCP group.

Based on the results of this study we believe both ERCP as well as cholecystectomy may be used for CBDS treatment in the elderly with acceptable safety.

Acknowledgements Open access funding provided by Uppsala University.

Compliance with ethical standards

Disclosures Drs. Syrén, Enochsson, Eriksson, Eklund, Isaksson and Sandblom have no conflicts of interest or financial ties to disclose.

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Paper IV

Abstract Outcome of ERCP related to case-volume 210403

Background and Aims: In some studies, high endoscopic retrograde cholangiopancreatography (ERCP) case-volume has been shown to correlate to high success rate in terms of successful cannulation and fewer adverse events. The aim of this study was to analyze the association between ERCP success and complications, and endoscopist and centre case-volumes.

Methods: Data were obtained from the Swedish National Register for Gallstone Surgery and ERCP (GallRiks) on all ERCPs performed for Common Bile Duct Stone (CBDS) (n=17873) and suspected or confirmed malignancy (n=6152) between 2009 and 2018. Successful cannulation rate, procedure time, intra- and postoperative complication rates and post-ERCP pancreatitis (PEP) rate, were compared with endoscopist and centre ERCP case-volumes during the year preceding the procedure as predictor.

Results: In multivariable analyses of the CBDS group adjusting for age, gender and year, a high endoscopist case-volume was associated with higher successful cannulation rate, lower complication and PEP rates, and shorter procedure time ($p<0.05$). Centres with a high annual case-volume were associated with high successful cannulation rate and shorter procedure time ($p<0.05$), but not lower complication and PEP rates.

When indication for ERCP was malignancy, a high endoscopist case-volume was associated with high successful cannulation rate and low PEP rates ($p<0.05$), but not shorter procedure time or low complication rate. Centres with high case-volume were associated with high successful cannulation rate and low complication and PEP rates ($p<0.05$), but not shorter procedure time.

Conclusions: The results suggest that higher endoscopist and centre case-volumes are associated with safer ERCP and successful outcome.

Outcome of ERCP related to case-volume

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard procedure to diagnose and treat conditions in the biliary and pancreatic ducts such as common bile duct stone (CBDS) and biliary tract malignancy. In unselected population-based settings, successful cannulation is achieved in >85% of cases [1, 2]. The complexity of ERCP, however, ranges from uncomplicated extraction of small stones to extremely challenging procedures such as hilar stenting, electrohydraulic lithotripsy (EHL) for difficult stones, and oral cholangioscopy or pancreatoscopy. ERCP complexity can be graded according to Schutz's criteria [3] or the Cotton classification [4]. The Cotton scale includes not only the complexity of the endoscopic procedure but also the experience of the endoscopist.

Existing complexity grading scales lack validation, and to be able to compare results from different endoscopic centres, and thereby allocate resources, a new ERCP complexity grading scale, the H.O.U.S.E. classification was designed and developed at the Karolinska University Hospital Huddinge in 2017. H.O.U.S.E. includes three ERCP categories: Category I, uncomplicated ERCP; Category II, ERCP of intermediate complexity: and Category III, highly complicated ERCP. The H.O.U.S.E. classification was shown to predict procedure time and to some extent adverse events [5].

Several complications are associated with ERCP the most common being post-ERCP pancreatitis (PEP) with a rate of 3.5-5% [1, 6-8]. The risk for developing PEP is correlated to technical factors, complexity of the procedure, and patient-related variables [7-13]. Although PEP is widely accepted as the primary adverse outcome measure following ERCP, the risk factors for PEP also are associated with other adverse events such as bleeding,

perforation, and other procedure-related complications. PEP may thus be considered a surrogate endpoint for safety and success of ERCP.

Lack of experience has been shown to be associated with poor outcome in major surgical procedures [14]. Likewise, larger ERCP case-volumes are associated with higher success rates in terms of successful cannulation and fewer complications [2, 15-20]. Studies have shown that high-volume ERCP centres have better results and lower complication rates than low-volume centres [16, 17, 21, 22]. However, there are also data showing that low-volume units can also perform safe ERCPs [23-25]. It is difficult to say whether theses conflicting results depend on the experience of the endoscopist or routines at the centres where the ERCPs are performed. Centralization of complex ERCPs to high-volume centres with highly experienced endoscopists may well increase the safety and success of this procedure. Population-based studies are needed to confirm this hypothesis.

The aim of this study was to compare highly and less experienced endoscopists as well as high and low-volume centres, regarding successful cannulation rates, procedure times, intraoperative complication rates, and postoperative complications rates within 30 days (PEP, perforation and intra- and postoperative bleeding), of ERCPs performed for common bile duct stone or malignancy.

MATERIALS AND METHODS

This study is based on data retrieved from the Swedish National Register for Gallstone Surgery and ERCP, GallRiks, which was created 2005 under direction of the Swedish National Board of Health and Welfare and the Swedish Surgical Society and administered by the Uppsala Clinical Research Center (UCR). GallRiks covers about 90% of cholecystectomies and

ERCPs performed in Sweden, and practically all Swedish hospitals participate. Most of these procedures are performed by surgeons, even if gastroenterologists are responsible for a smaller proportion of ERCPs. Patient- and procedure-related data as well as intraoperative complications and postoperative complications within 30 days are prospectively registered. The completeness of 30-day follow-up is approximately 95%. GallRiks is regularly validated, and the validation process and the results of national coverage are published each year [1, 26-28]. Consent from the patient to participate in register-based research is required for registration in GallRiks. Patients are able to withdraw their personal data from the register at any time. PEP was defined as: 1. typical abdominal pain; 2. serum amylase elevation >3 times the upper limit longer than 24 h after ERCP; and 3. need for hospitalization according to the Cotton criteria [7].

Data from GallRiks on all ERCPs 2009-2018 performed for common bile duct stone (n=17873) and malignancy (n=6152), with complete registration and 30-day follow-up, were collected and compiled. Procedures for any other indication, procedures on patients having undergone previous ERCP since 2006, and rendezvous ERCPs were excluded from the analysis (*Fig 1*). Associations between both endoscopist ERCP case-volume and centre volume, and successful cannulation rate, procedure time, intraoperative complication rate, and postoperative complication rate within 30 days (PEP, perforation, and intra- and postoperative bleeding) were analyzed. Volumes were based on those during the year preceding the observations. When calculating cumulative volume of ERCP procedures for endoscopists and centers no ERCPs were excluded.

STATISTICS

Univariable and multivariable logistic regression analyses with the endpoints successful cannulation, procedure time, intraoperative complication rate, and postoperative complication rate within 30 days (PEP, perforation, and intra- and postoperative bleeding) were performed with endoscopist and centre volumes as the variables. In the multivariable logistic regression analyses, adjustments were made for gender, age, and year of ERCP. The adjustments made in the multivariable analysis were based on assumptions of cause-effect relationships. Analyses were made with volumes on log scales (n=0-4, 5-10, 11-20, 21-40, 41-80, 81-160 or 161-320 for endoscopist and n=0-20, 21-40, 41-80, 81-160, 161-320 or >320 for centre).

RESULTS

ERCP for CBDS was more common in women (58.7%). Mean age of patients undergoing ERCP for CBDS was 67.1 years. ERCP for malignancy was more equally distributed between the sexes, mean age being 71.6 years. The proportion of procedures performed by an endoscopist with an ERCP case-volume >80 the preceding year increased from 37% in 2009 to 40% in 2018. The proportion of procedures performed at a centre with an ERCP volume >160 the preceding year increased from 70% in 2009 to 78% in 2018 (*Table 1*). Regarding degrees of complexity of ERCPs performed by endoscopists and at centres with different procedure volumes, no major changes occurred during the study period. Procedures classified as H.O.U.S.E. II or III were performed at centres with a procedure volume >160 in 71% (n=1179) in 2009 and 83% (n=1493) in 2018. The percentage of procedures classified as

H.O.U.S.E. II or III performed by endoscopists with an ERCP case-volume >80 increased from 41% (n=689) in 2009 to 47% (n=851) in 2018.

Regarding ERCP for CBDS, higher endoscopist ERCP case-volume as well as centre volume were correlated to higher rate of successful deep cannulation of the bile duct, shorter procedure time, lower intraoperative complication rate, lower postoperative complication rate within 30 days, and lower PEP rate. In the multivariable analysis gender was not significant when it came to procedure time (*Table 2, Fig 2*).

Regarding ERCP for malignancy, results were not as clear as for ERCP performed for CBDS. Higher endoscopist volume and centre volume correlated with a higher rate of successful deep cannulation of the bile duct, but not to shorter procedure time. Intraoperative complication rate, postoperative complication rate within 30 days, and PEP rate were lower at high-volume centres but endoscopist case-volume showed no correlation (*Table 3, Fig 3*).

DISCUSSION

In this study, based on prospectively retrieved data over a period of 10 years, the association between ERCP case-volume, both endoscopist and centre, and successful cannulation, procedure time and adverse events, were analyzed. This study focused on two well-established indications for ERCP; CBDS and malignancy. The results show that acquired experience has a great impact on ERCP outcome for the endoscopist, especially when performed for CBDS. The pattern was not so clear for procedures performed for suspected malignancy. At the centre level, annual volume was also associated with better outcome.

A limitation of this study is the accuracy of registration of data. Registration of incorrect indication and incompleteness and low frequency of 30-day follow-up affect results and outcome. Until recently, for example, it was possible to select jaundice as an indication for ERCP in GallRiks, rather than the specific condition such as CBDS or malignancy. In order to obtain a homogenous study population, we excluded all procedures carried out with unclear indication, which to some extent limits the external validity. Regarding complicated ERCP procedures, postoperative complication rate have been shown to be higher in units with a more meticulous follow-up [29]. As yet, GallRiks has not been linked to the Swedish National Patient Register (NPR), so some complications, particularly those occurring after 30 days, may have been missed. However, it is more likely that most adverse events following ERCP occur in the immediate postoperative period.

Choledocholithiasis is the most common indication for ERCP, and procedures for this indication are performed at almost all hospitals in Sweden [1, 26]. Furthermore, the most common management of CBDS detected by cholangiography during cholecystectomy is intraoperative rendezvous ERCP [1, 30]. In these cases, access to the bile duct is facilitated by an antegrade guidewire from the cystic duct to the duodenum, and the rate of unsuccessful perioperative complications, particularly PEP, is low. We therefore chose to exclude rendezvous ERCPs [31, 32]. Non-rendezvous ERCPs performed for CBDS may be complicated; large impacted stones, for example, that require advanced methods such as electrohydraulic lithotripsy (EHL). The majority of ERCPs for CBDS, however, are uncomplicated and fall into the H.O.U.S.E. category I [5] or Cotton and Schutz Grade II [3, 4]. Endoscopists with the greatest experience and centres with the highest volumes had the highest cannulation success rate, shortest procedure times, and lowest complication rates when the indication for ERCP was CBDS.

Results of ERCPs for malignancy did not show the same clear pattern as for CBDS. Even if successful cannulation was more common for high-volume endoscopists and centres, procedure times were longer and complication rates, including PEP, were paradoxically higher for endoscopists who performed many ERCPs. ERCP for the diagnosis and treatment of malignancy is often more complicated than ERCP for CBDS, especially if the malignancy is intrahepatic. These procedures are associated with greater risk and higher adverse event rates. ERCP for malignancy is graded at least H.O.U.S.E. II, Schutz IV or Cotton III [3-5]. The paradoxal results of ERCPs performed for malignancy by more experienced endoscopists, with longer procedure times and higher complication rates, may be explained by selection bias. In general, the most experienced high-volume endoscopist performs the most complex and time-consuming ERCP procedures that have the greatest risks for adverse events. Furthermore, high-volume endoscopists use more advanced ERCP techniques such as needle-knife sphincterotomy, and are more likely to persevere longer and spend greater effort cannulating the bile duct before giving up [33].

Case-volume is an important issue in ERCP-training, and it is important that the training of future advanced endoscopists is carried out at high-volume center-volume centres. The learning curve among trainees in advanced endoscopy varies significantly. The success rates of trainees performing ERCP, however, increase with increasing experience [34, 35].

This study suggests that greater endoscopist experience and higher centre case-volume are associated with safer and more successful ERCP performance.

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Figure 1. Flow chart showing study group assembly.

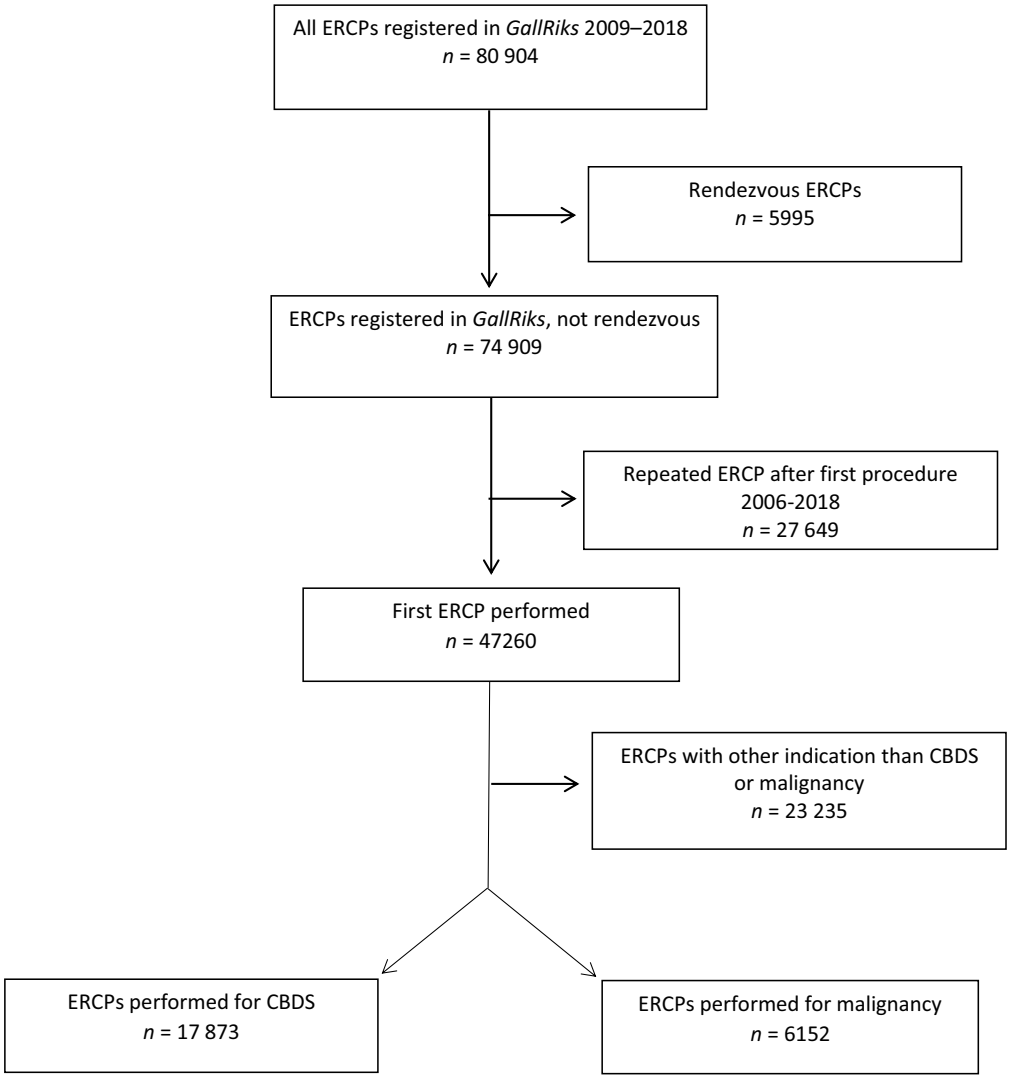
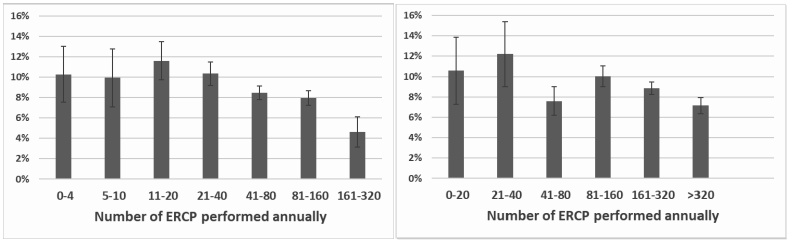


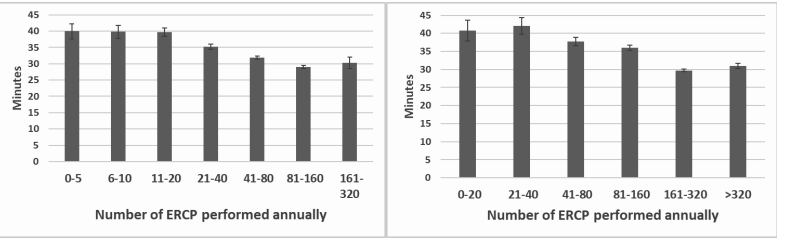
Figure 2. ERCPs 2009-2018 with indication common bile duct stone. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct (in this figure illustrated as unsuccessful deep cannulation), intra- and postoperative complications within 30 days and post-ERCP pancreatitis (PEP) as outcome. A=Endoscopist, B=Centre

A B



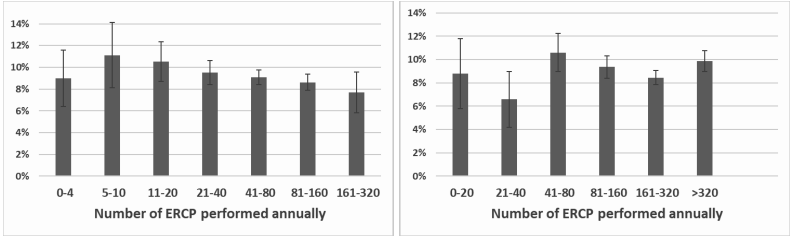
Unsuccessful deep cannulation of bile duct

A B



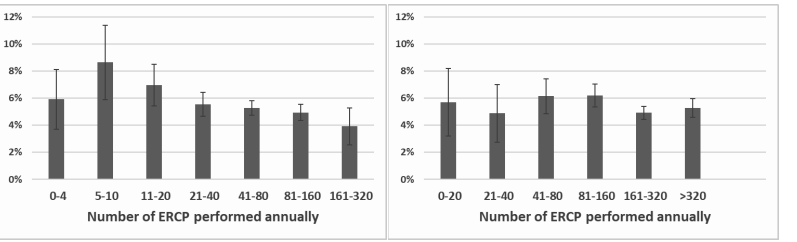
Procedure time

A B



Intra- and postoperative complications within 30 days

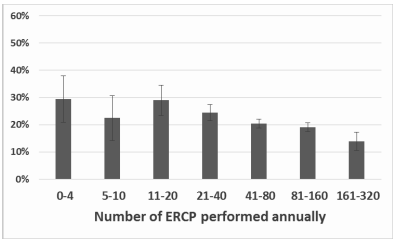
A B



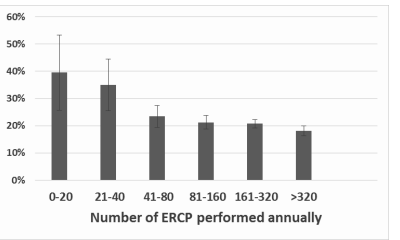
Post-ERCP pancreatitis

Figure 3. ERCPs 2009-2018 with indication malignancy. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct (in this figure illustrated as unsuccessful deep cannulation), intra- and postoperative complications within 30 days and post-ERCP pancreatitis (PEP) as outcome. A=Endoscopist, B=Centre

A

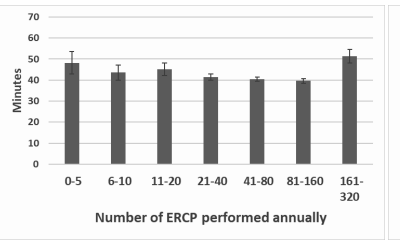


B



Unsuccessful deep cannulation of bile duct

A



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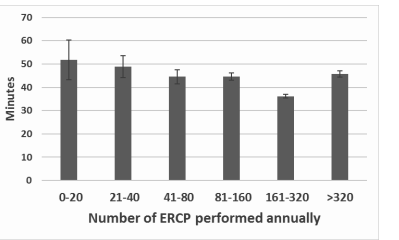
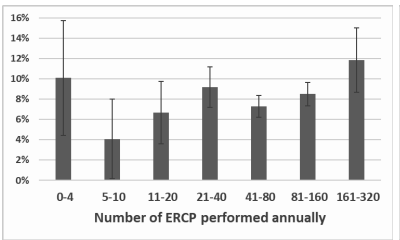


Procedure time

A



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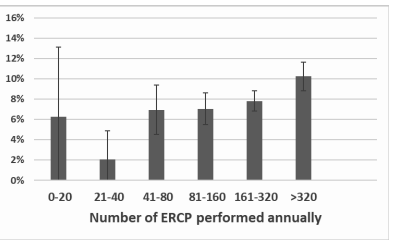
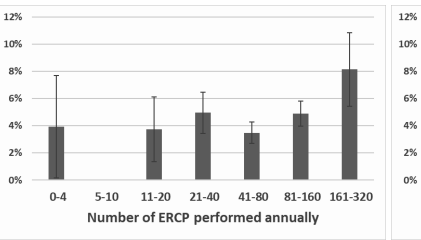


Intra- and postoperative complications within 30 days

A



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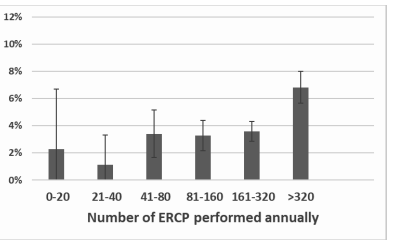

Post-ERCP pancreatitis

Table 1. Baseline characteristics of the cohort 2009-2018

	ERCP for common bile duct stones (N=17873)	ERCP for malignancy (N=6152)
Gender		
Men	7373 (41.3%)	2944 (47.9%)
Women	10492 (58.7%)	3206 (52.1%)
Unknown	8 (<0.01%)	2 (<0.01%)
Mean age, years	67.1 (y)	71.6 (y)
Year of ERCP		
2009	1260 (7.0%)	538 (8.7%)
2010	1786 (10.0%)	497 (8.1%)
2011	1872 (10.5%)	515 (8.4%)
2012	1757 (9.8%)	559 (9.1%)
2013	1799 (10.1%)	613 (10.0%)
2014	1905 (10.7%)	583 (9.5%)
2015	1905 (10.7%)	652 (10.6%)
2016	1924 (10.8%)	783 (12.7%)
2017	1881 (10.5%)	669 (10.9%)
2018	1784 (10.0%)	743 (12.1%)
Number of ERCPs performed by endoscopist previous year		
0-5	467 (2.6%)	109 (1.8%)
6-10	423 (2.4%)	98 (1.6%)
11-20	1111 (6.2%)	255 (4.1%)
21-40	2726 (15.3%)	816 (13.3%)
41-80	6884 (38.5%)	2230 (36.2%)
81-160	5483 (30.7%)	2247 (36.5%)
161-320	779 (4.4%)	397 (6.5%)
Number of ERCPs performed at centre previous year		
0-5	50 (0.3%)	8 (0.1%)
6-10	76 (0.4%)	6 (0.1%)
11-20	215 (1.2%)	34 (0.6%)
21-40	410 (2.3%)	97 (1.6%)
41-80	1368 (7.7%)	418 (6.8%)
81-160	3398 (19.0%)	1050 (17.1%)
161-320	8098 (45.3%)	2712 (44.1%)
>320	4258 (23.8)	1827 (29.7%)

Table 2. ERCPs 2009-2018 with indication common bile duct stone. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct, intra- and postoperative complications within 30 days and post-ERCP pancreatitis (PEP) as outcomes.

Endoscopist case-volume					**Centre case-volume**				
Outcome	Univariable		Multivariable		Outcome	Univariable		Multivariable	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Successful deep cannulation of bile duct									
Endoscopist annual ERCP volume	1.187 (1.172-1.202)	**<0.001**	1.093 (1.078-1.108)	**<0.001**	Centre annual ERCP volume	1.083 (1.037-1.131)	**<0.001**	1.084 (1.038-1.133)	**<0.001**
Women (reference men)	1.112 (1.072-1.153)	**<0.001**	1.116 (1.076-1.158)	**<0.001**	Women (reference men)	1.112 (1.072-1.153)	**<0.001**	1.110 (0.999-1.233)	0.053
Age (years)	0.997 (0.996-0.998)	**<0.001**	0.997 (0.996-0.998)	**<0.001**	Age (years)	0.997 (0.996-0.998)	**<0.001**	0.995 (0.992-0.998)	**0.002**
Year of ERCP	1.015 (1.010-1.021)	**<0.001**	1.012 (1.007-1.017)	**<0.001**	Year of ERCP	1.015 (1.010-1.021)	**<0.001**	0.998 (0.980-1.017)	0.846
Intra- and postoperative complications within 30 days									
Endoscopist annual ERCP volume	0.951 (0.913-0.990)	**0.015**	0.950 (0.912-0.989)	**0.013**	Centre annual ERCP volume	1.007 (0.962-1.053)	0.775	1.006 (0.961-1.053)	0.794
Women (reference men)	1.164 (1.048-1.292)	**0.005**	1.134 (1.020-1.261)	**0.020**	Women (reference men)	1.164 (1.048-1.292)	**0.005**	1.133 (1.019-1.259)	**0.021**
Age (years)	0.992 (0.989-0.995)	**<0.001**	0.992 (0.989-0.995)	**<0.001**	Age (years)	0.992 (0.989-0.995)	**<0.001**	0.992 (0.989-0.995)	**<0.001**
Year of ERCP	1.014 (0.996-1.033)	0.126	1.02 (0.99995-1.037)	0.051	Year of ERCP	1.014 (0.996-1.033)	0.126	1.018 (0.999-1.037)	0.058
Post-ERCP pancreatitis									
Endoscopist annual ERCP volume	1.044 (1.018-1.070)	**<0.001**	1.028 (1.002-1.054)	0.034	Centre annual ERCP volume	0.953 (0.901-1.009)	0.099	0.954 (0.902-1.010)	0.103
Women (reference men)	1.267 (1.188-1.351)	**<0.001**	1.251 (1.173-1.334)	**<0.001**	Women (reference men)	1.267 (1.188-1.351)	**<0.001**	1.311 (1.137-1.511)	**<0.001**
Age (years)	0.982 (0.981-0.984)	**<0.001**	0.983 (0.981-0.985)	**<0.001**	Age (years)	0.982 (0.981-0.984)	**<0.001**	0.983 (0.980-0.987)	**<0.001**
Year of ERCP	1.036 (1.027-1.046)	**<0.001**	1.034(1.025-1.043)	**<0.001**	Year of ERCP	1.036 (1.027-1.046)	**<0.001**	1.011 (0.987-1.035)	0.382
Procedure duration (minutes)									
	Standardized coefficient beta	p	Standardized coefficient beta	p		Standardized coefficient beta	p	Standardized coefficient beta	p
Endoscopist annual ERCP volume	-2.574 (-2.824- -2.323))	**<0.001**	-2.579 (-2.828- -2.330)	**<0.001**	Centre annual ERCP volume	-2.523 (-2.796- -2.250)	**<0.001**	-2.583 (-2.855- -2.310)	**<0.001**
Women (reference men)	-0.121 (-0.751-0.509)	0.706	0.369 (-0.255-0.993)	0.246	Women (reference men)	-0.121 (-0.751-0.509)	0.706	0.286 (-0.339-0.911)	0.370
Age (years)	0.083 (0.066-0.100)	**<0.001**	0.081 (0.064-0.097)	**<0.001**	Age (years)	0.083 (0.066-0.100)	**<0.001**	0.081 (0.065-0.098)	**<0.001**
Year of ERCP	0.277 (0.165-0.3881)	**<0.001**	0.274 (0.164-0.384)	**<0.001**	Year of ERCP	0.277 (0.165-0.3881)	**<0.001**	0.330 (0.220-0.441)	**<0.001**

Table 3. ERCPs 2009-2018 with indication malignancy. Univariable and multivariable linear regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with procedure duration as outcome. Univariable and multivariable logistic regression analyses of ERCP volumes (endoscopist and centre) during the year preceding the procedure with successful deep cannulation of bile duct, intra- and postoperative complications within 30 days and post-ERCP pancreatitis (PEP) as outcomes.

Endoscopist case-volume					**Centre case-volume**				
Outcome	Univariable		Multivariable		Outcome	Univariable		Multivariable	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p		Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Successful deep cannulation of bile duct									
Endoscopist annual ERCP volume	1.158 (1.100-1.218)	**<0.001**	1.155 (1.097-1.216)	**<0.001**	Centre annual ERCP volume	1.153 (1.088-1.222)	**<0.001**	1.143 (1.078-1.212)	**<0.001**
Women (reference men)	1.007 (0.890-1.140)	0.907	1.029 (0.908-1.166)	0.655	Women (reference men)	1.007 (0.890-1.140)	0.907	1.029 (0.908-1.166)	0.653
Age (years)	0.993 (0.988-0.999)	0.018	0.994 (0.988-0.999)	**0.020**	Age (years)	0.993 (0.988-0.999)	0.018	0.994 (0.988-0.999)	0.027
Year of ERCP	1.024 (1.002-1.046)	0.032	1.024(1.002-1.046)	0.033	Year of ERCP	1.024 (1.002-1.046)	0.032	1.021 (0.999-1.043)	0.065
Intra- and postoperative complications within 30 days									
Endoscopist annual ERCP volume	1.068 (0.984-1.159)	0.118	1.062 (0.978-1.153)	0.151	Centre annual ERCP volume	1.206 (1.092-1.331)	**<0.001**	1.186 (1.074-1.309)	**0.001**
Women (reference men)	1.071 (0.893-1.285)	0.461	1.105 (0.920-1.328)	0.285	Women (reference men)	1.071 (0.893-1.285)	0.461	1.105 (0.920-1.328)	0.285
Age (years)	0.989 (0.981-0.996)	**0.002**	0.988 (0.981-0.996)	**<0.001**	Age (years)	0.989 (0.981-0.996)	**0.002**	0.989 (0.982-0.997)	**0.004**
Year of ERCP	1.036 (1.004-1.070)	0.029	1.037 (1.004-1.071)	0.027	Year of ERCP	1.036 (1.004-1.070)	0.029	1.032 (1.000-1.066)	0.052
Post-ERCP pancreatitis									
Endoscopist annual ERCP volume	1.190 (1.056-1.341)	**0.004**	1.179 (1.045-1.330)	**0.008**	Centre annual ERCP volume	1.425 (1.230-1.651)	**<0.001**	1.362 (1.174-1.579)	**<0.001**
Women (reference men)	1.220 (0.949-1.567)	0.120	1.313 (1.020-1.692)	0.035	Women (reference men)	1.220 (0.949-1.567)	0.120	1.303 (1.011-1.679)	0.041
Age (years)	0.974 (0.965-0.984)	**<0.001**	0.973 (0.963-0.982)	**<0.001**	Age (years)	0.974 (0.965-0.984)	**<0.001**	0.974 (0.965-0.984)	**<0.001**
Year of ERCP	1.117 (1.067-1.169)	**<0.001**	1.122 (1.072-1.175)	**<0.001**	Year of ERCP	1.117 (1.067-1.169)	**<0.001**	1.114 (1.064-1.167)	**<0.001**
Procedure duration (minutes)									
	Standardized coefficient beta	p	Standardized coefficient beta	p		Standardized coefficient beta	p	Standardized coefficient beta	p
Endoscopist annual ERCP volume	-0.207 (-0.768-0.354)	0.470	-0.288 (-0.848-0.271)	0.312	Centre annual ERCP volume	-0.365 (-1.000-0.270)	0.260	-0.637 (-1.274- -0.001)	0.050
Women (reference men)	-1.737 (-3.026- -0.448)	0.008	-1.607 (-2.899--0.314)	0.015	Women (reference men)	-1.737 (-3.026--0.448)	0.008	-1.614 (-2.907--0.322)	0.014
Age (years)	-0.098 (-0.153- -0.042)	**0.001**	-0.100 (-0.155- -0.044)	**<0.001**	Age (years)	-0.098 (-0.153--0.042)	**0.001**	-0.102 (-0.158- -0.047)	**<0.001**
Year of ERCP	0.724 (0.500-0.949)	**<0.001**	0.741 (0.516-0.965)	**<0.001**	Year of ERCP	0.724 (0.500-0.949)	**<0.001**	0.758 (0.533-0.984)	**<0.001**